



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 277/64, A61K 31/425, C07D 277/66, 417/14, 235/06, 249/18, 417/12		A1	(11) International Publication Number: WO 94/22846 (43) International Publication Date: 13 October 1994 (13.10.94)
(21) International Application Number: PCT/US94/01724		(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).	
(22) International Filing Date: 28 February 1994 (28.02.94)		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(30) Priority Data: 08/040,233 30 March 1993 (30.03.93)		US	Published <i>With international search report.</i>
(60) Parent Application or Grant (63) Related by Continuation US Filed on 08/040,233 (CIP) 30 March 1993 (30.03.93)			
(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): ARNOLD, Lee, D. [CA/US]; 256 Bloomingdale Road, Quaker Hill, CT 06375 (US). COE, Jotham, W. [US/US]; 151 Lamphere Road, Mystic, CT 06355 (US). KANEKO, Takushi [JP/US]; 398 Northwood Drive, Guilford, CT 06437 (US). MOYER, Mikel, P. [US/US]; 16 Christopher Lane, Clinton, CT 06413 (US).			

(54) Title: COMPOUNDS ENHANCING ANTITUMOR ACTIVITY OF OTHER CYTOTOXIC AGENTS

(57) Abstract

This invention relates to certain heterocyclic compounds and their pharmaceutically acceptable salts, which are useful for sensitizing multidrug-resistant tumor cells to anticancer agents and multidrug resistant forms of malaria, tuberculosis, leishmania and amoebic dysentery to chemotherapeuticants. The compounds and their pharmaceutically acceptable salts are also inhibitors of the active drug transport capability of P-glycoprotein which is encoded by the human *MDR1* gene, as well as of certain other related ATP-binding-cassette transporters from eukaryotic and prokaryotic organisms (e.g., *pfmdr* from *Plasmodium falciparum*, and murine *mdrl* and *mdr3* gene products).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

COMPOUNDS ENHANCING ANTITUMOR ACTIVITY OF OTHER CYTOTOXIC
AGENTS

5

Background of the Invention

This invention relates to certain heterocyclic compounds and their use as sensitizers of tumor cells to anticancer agents and sensitizers of multidrug resistant forms of malaria (Plasmodium falciprum), tuberculosis, leishmania and amoebic dysentery. The compounds are also useful in facilitating delivery of cancer 10 chemotherapeuticants and other drugs across the blood-brain barrier, treatment of AIDS (especially in enhancing intracellular accumulation of drugs in infected lymphocytes) in humans and sensitization of multidrug resistant infections in humans and animals (especially Eimerian coccidial).

In cancer chemotherapy the effectiveness of anticancer drugs is often limited by 15 the resistance of tumor cells. Some tumors such as of the colon, pancreas, kidney and liver are generally innately resistant, and other responding tumors often develop resistance during the course of chemotherapy. The phenomena of multidrug resistance (MDR) is typically characterized by the tumor cell's cross-resistance to adriamycin, daunomycin, vinblastine, topotecan, teniposide, vincristine, taxol, actinomycin D and 20 etoposide. The resistance of cells is often associated with overexpression of the *MDR1* gene. This gene encodes for a 140-220 kd trans-membrane phosphoglycoprotein (P-glycoprotein) which functions as an ATP-dependent efflux pump. Thus, it has been postulated that this efflux mechanism keeps the intracellular level of the anticancer drug low, allowing the tumor cells to survive.

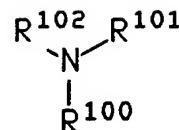
25 In recent years various substances such as verapamil, nifedipine trifluoroperazine, and diltiazem have been used in in vitro experimental systems to reverse the MDR phenomena. More recently some of these agents have been tested clinically as MDR reversing agents. Little efficacy has been observed with verapamil or trifluoroperazine. Thus, there is a need for an effective MDR reversing agent.

30 Quinoline derivatives and other related compounds are claimed as anti-cancer drug reinforcing agents in European Patent Application 0 363 212.

Summary of the Invention

The compounds of the present invention are of the formula

-2-

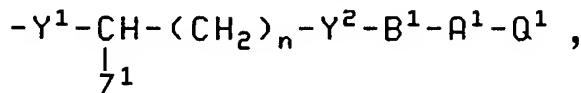


5

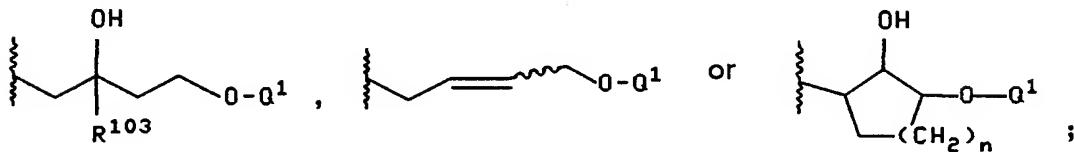
(I)

and the pharmaceutically acceptable acid addition salts thereof wherein R^{100} is

10



15



where R^{103} is $-(\text{C}_1-\text{C}_4)\text{alkyl}$;

Y^1 is selected from the group consisting of oxygen, methylene, ethylene and a covalent bond;

20

Z^1 is selected from the group consisting of H, OH, CF_3 , NO_2 , and $-\text{O}(\text{C}_1-\text{C}_4)\text{alkyl}$;

n is 1 or 2;

Y^2 is selected from the group consisting of O, S, NH, NCH_3 , a covalent bond,

25



B^1 is selected from the group consisting of a covalent bond and optionally substituted phenyl,

30

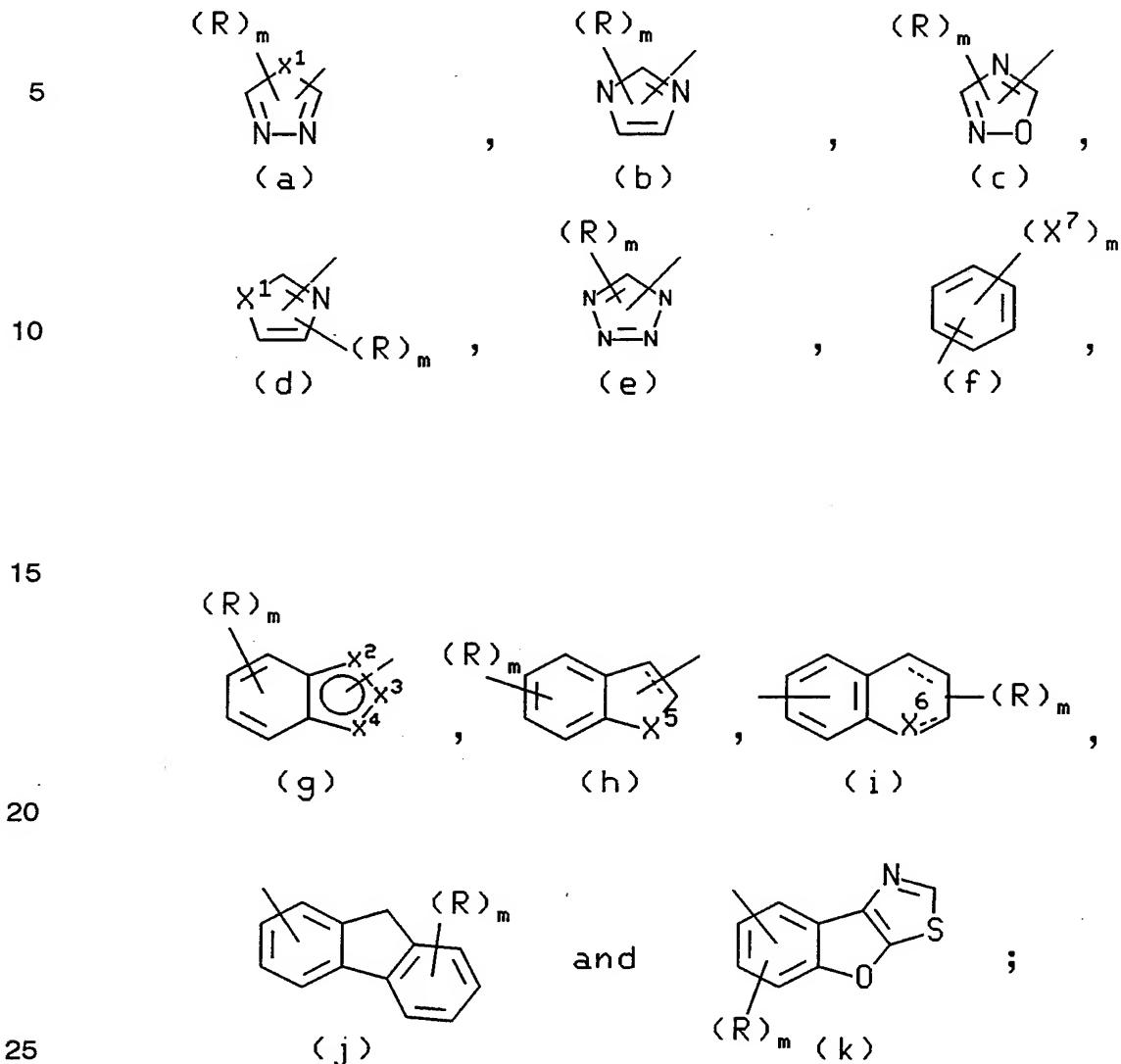
where the optionally substituted phenyl is optionally substituted with one or two substituents independently selected from the group consisting of $(\text{C}_1-\text{C}_4)\text{alkyl}$, halo, $(\text{C}_1-\text{C}_4)\text{alkoxy}$, amino, N-alkylamino having 1 to 4 carbons, N,N-dialkylamino having a total of 2 to 4 carbons, nitrile and nitro;

A^1 is selected from the group consisting of a covalent bond, $(\text{C}_1-\text{C}_4)\text{alkylene}$, O, S and NH;

35

-3-

Q¹ is selected from the group consisting of

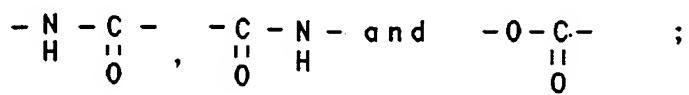


wherein _____ represents a single or a double bond;

X^1 is O or S;

X^2 , X^3 and X^4 are each independently selected from the group consisting of C, N, CH, NH, O and S, provided that no more than one of X^2 , X^3 and X^4 is O or S;

X^5 is selected from the group consisting of



-4-

5 X^6 is selected from the group consisting of C, CH, N, NH,



15 X^7 is selected from the group consisting of (C₁-C₄)alkyl, halo, (C₁-C₄)alkoxy, amino, nitrile, nitro, N-alkylamino having 1 to 4 carbons and N,N-dialkylamino having a total of 2 to 6 carbons;

20 m is 1, 2 or 3;

15 and each R is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo, N-alkylamino having 1 to 4 carbons, N,N-dialkylamino having a total of 2 to 6 carbons, amino, nitro, nitrile, hydroxyl, alkylthio having 1 to 3 carbons, =N-OCH₃, =N-OH, pyridinyl, (pyridin-1-yl)methylene, piperazinyl, 4-alkylpiperazinyl having 1 to 4 carbons in the alkyl portion, morpholino, -CH₂-C(OH)(CH₃)₂, allyl, -NHCOCH₃, aralkylamino having 1 to 4 carbons in the alkyl portion and optionally substituted phenyl,

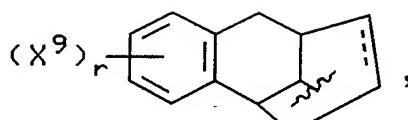
25 where the optionally substituted phenyl is optionally substituted with 1 or 2 substituents independently selected from the group consisting of (C₁-C₄)alkyl, halo, (C₁-C₄)alkoxy, amino, nitrile, nitro, N-alkylamino having 1 to 4 carbons and N,N-dialkylamino having a total of 2 to 6 carbons;

30 R¹⁰¹ is the same as R¹⁰⁰ or is selected from the group consisting of hydrogen, (C₁-C₄)alkyl, alkenylphenyl having 2 to 4 carbons in the alkenyl portion, and alkylphenyl having 1 to 4 carbons in the alkyl portion and the phenyl portion is optionally substituted with one or two substituents independently selected from the group consisting of (C₁-C₄)alkyl, halo, (C₁-C₄)alkoxy, amino, nitrile, nitro, N-alkylamino having 1 to 4 carbons and N,N-dialkylamino having a total of 2 to 6 carbons;

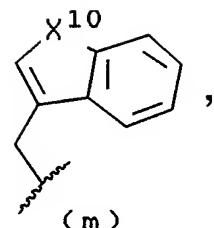
R¹⁰² is selected from the group consisting of hydrogen,

-5-

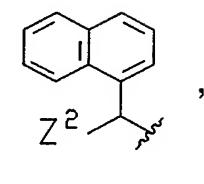
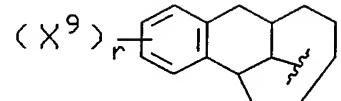
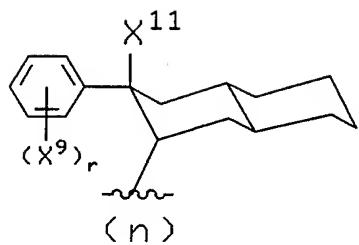
5



(l)



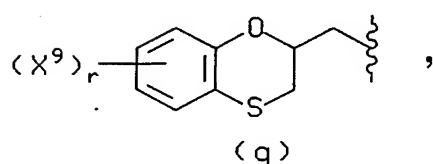
10



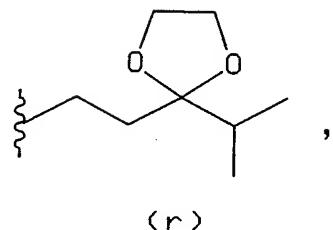
(o)

(p)

15

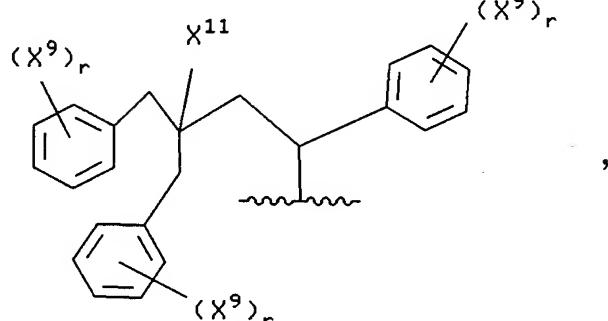
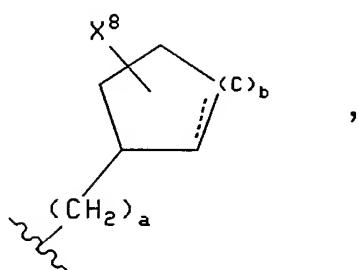


20



(r)

25



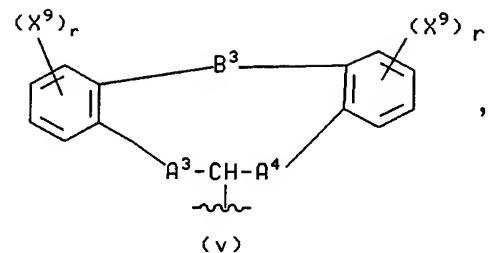
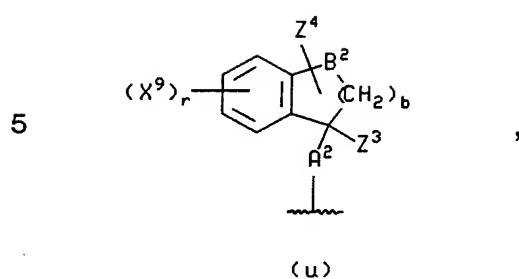
30

(s)

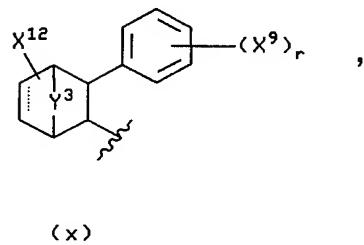
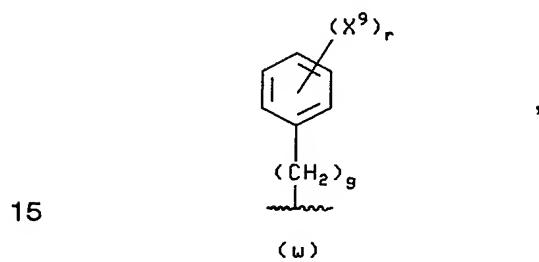
(t)

35

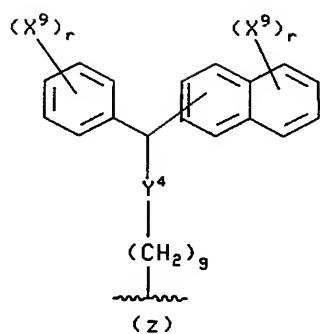
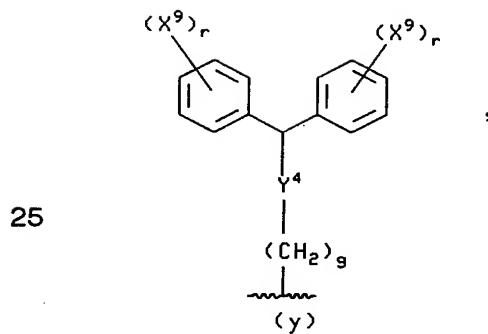
-6-



10



20

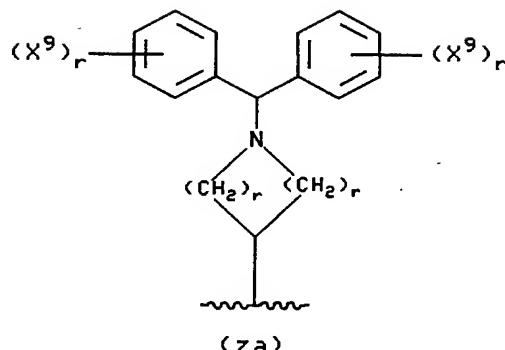


30

35

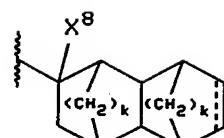
-7-

5

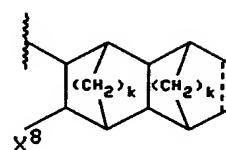


10

15



and



20

where r for each occurrence is independently 1 or 2;

a is 0, 1, 2 or 3;

X⁸ is selected from the group consisting of (C₁-C₄)alkyl and

25



where r is as defined above;

30

X⁹ for each occurrence is independently selected from the group consisting of hydrogen, hydroxy, chloro, fluoro, (C₁-C₄)alkoxy, CF₃ and (C₁-C₄)alkyl;

X¹⁰ is S or O;

X¹¹ is hydrogen or hydroxy;

Z² is hydrogen or methyl;

35

b is 0, 1, 2 or 3;

-8-

A² is selected from the group consisting of a covalent bond, CHCH₃ and (C₁-C₄)alkylene;

B² is selected from the group consisting of CH₂, CH and S;

5 Z³ is selected from the group consisting of hydrogen, phenyl and hydroxy;

Z⁴ is selected from the group consisting of hydrogen, phenyl and (C₁-C₄)alkyl;

B³ is selected from the group consisting of S, O, -CH₂O-, -CH₂S-, -CH₂-, -CH₂-CH₂-, -CH=CH- and no bond;

A³ and A⁴ are independently a covalent bond or methylene;

10 X¹² is selected from the group consisting of hydrogen, (C₁-C₄)alkyl, phenyl and benzyl;

Y³ is selected from the group consisting of (C₁-C₄)alkylene, O, S, -CH₂O- and -CH₂S-;

Y⁴ is selected from the group consisting of S, O, NH and a covalent bond;

15 g is an integer from 1 to 4;

k for each occurrence is independently 0, 1 or 2; and

 represents a single or a double bond;

or R¹⁰¹ and R¹⁰² are taken together with the nitrogen to which they are attached and form heterocycles selected from the group consisting of

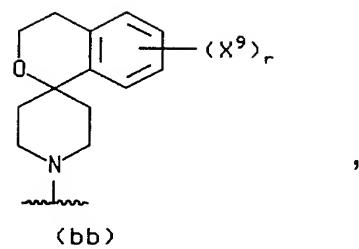
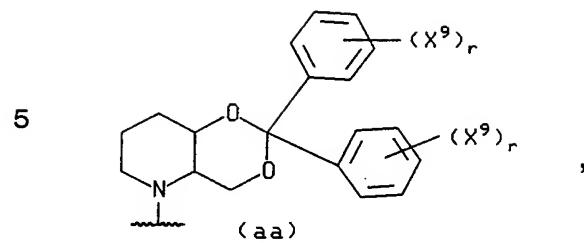
20

25

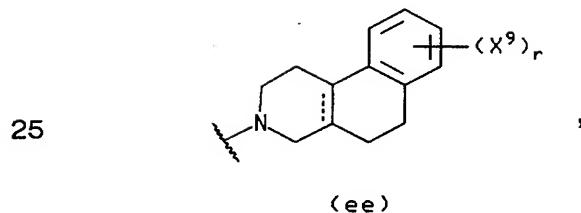
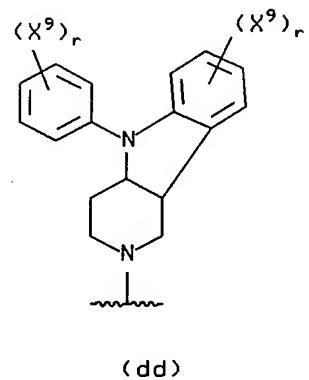
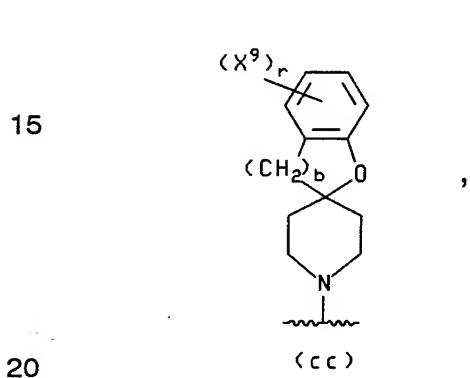
30

35

-9-



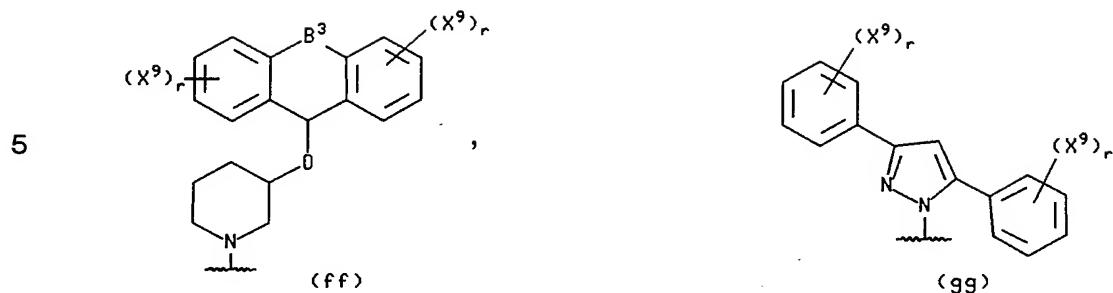
10



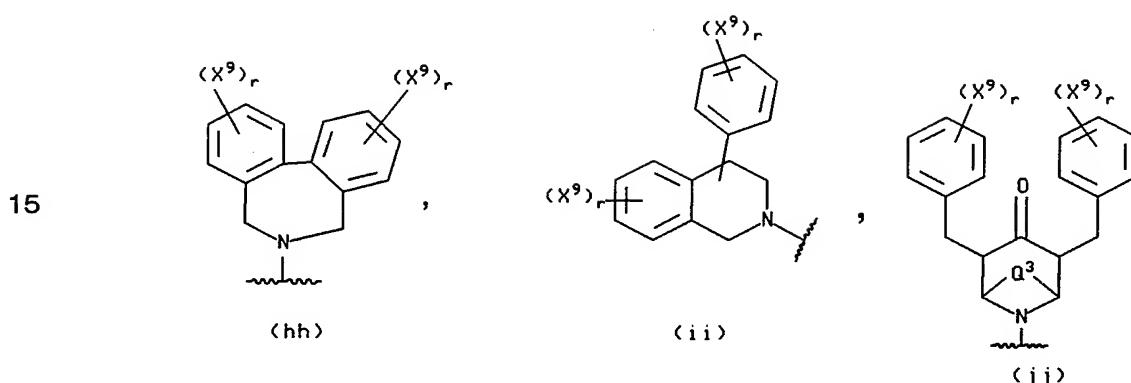
30

35

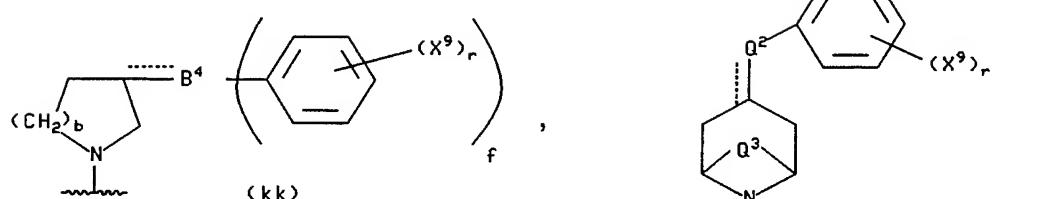
-10-



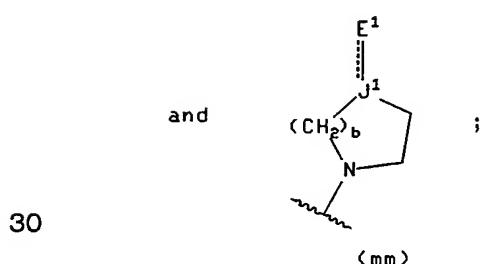
10



20



25



30

where X^9 , b , B^3 and r are as defined above;

Q^2 is selected from the group consisting of S, O, CH_2 and CH;

Q^3 is (C_1-C_4) alkylene;

35 B^4 is selected from the group consisting of C, O, $CH-CN$, CH and CH_2 ;

-11-

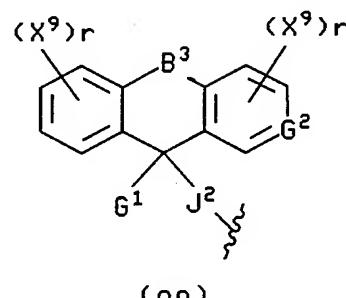
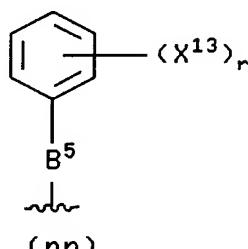
f is 1 or 2;

J¹ is selected from the group consisting of C, CH, and N;

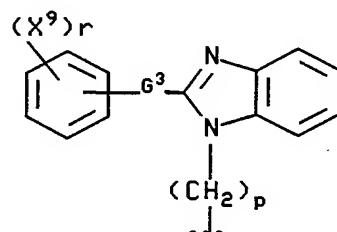
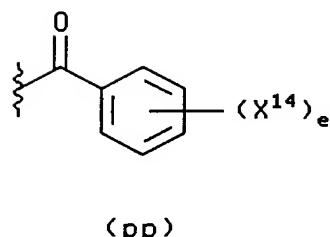
— represents a single or a double bond,

5 and E¹ is selected from the group consisting of alkylphenyl having 1 to 4 carbons,

10



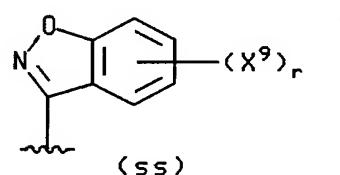
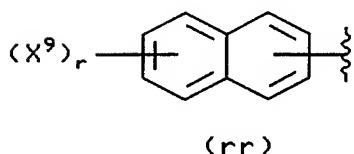
15



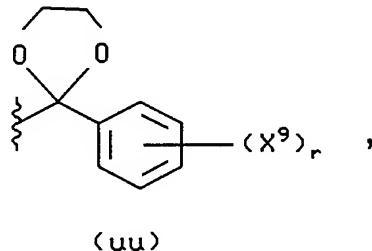
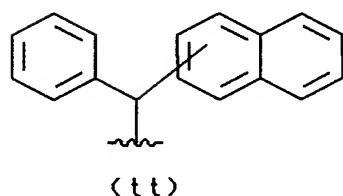
20

(qq)

25

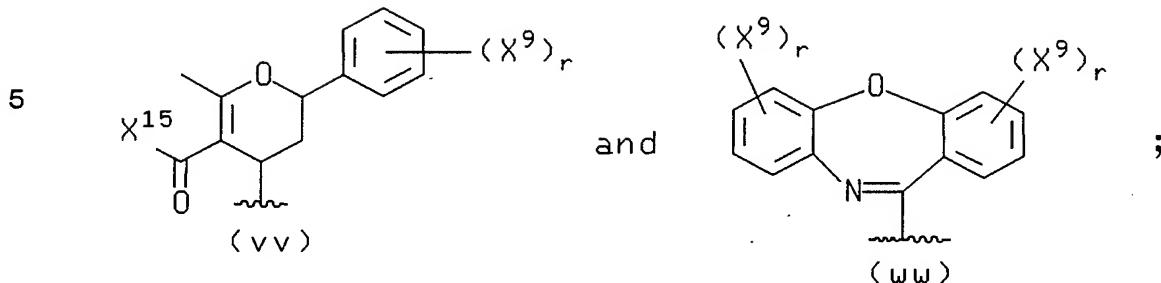


30



35

-12-



10

where X^9 , B^3 and r are as defined above;

B^5 is O, S, a covalent bond, CH, C=O, or (C_1-C_3) alkylene;

X^{13} is selected from the group consisting of hydrogen, hydroxy, chloro, fluoro, (C_1-C_4) alkoxy, CF_3 , (C_1-C_4) alkyl and thioalkyl having 1 to 4 carbons;

15

G^1 is hydrogen, CN or hydroxy;

G^2 is N or CH;

J^2 is selected from the group consisting of C=O, a covalent bond and (C_1-C_4) alkylene;

20

X^{14} is, for each occurrence, independently (C_1-C_4) alkyl;

e is 2, 3, 4 or 5;

G^3 is $\begin{array}{c} O \\ || \\ -NH-C- \end{array}$ or $\begin{array}{c} O \\ || \\ -C-NH- \end{array}$;

25

and p is 2 or 3;

provided that:

(1) when Y^1 is a covalent bond or when n is 0, Z^1 cannot be hydroxy, NO_2 , $-S(C_1-C_4)$ alkyl or $-O(C_1-C_4)$ alkyl;

(2) B^1 and A^1 cannot each be a covalent bond;

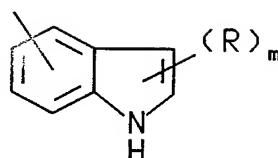
30 (3) when B^1 is an optionally substituted phenyl, Q^1 is selected from the group consisting of structures (a), (b), (c), (d), (e), (f), and (g);

(4) R^{101} and R^{102} cannot both be hydrogen at the same time;

(5) when B^1 is a covalent bond and Y^2 is O, S, NH or $\begin{array}{c} -C-N- \\ || \\ H \\ || \\ O \end{array}$, A^1 is not O, S or NH;

35

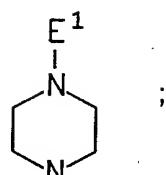
-13-

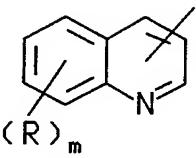
5 (6) when Q^1 is  , R^{101} and R^{102} taken together with the nitrogen to

5

10 which they are attached cannot be

10

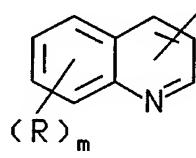


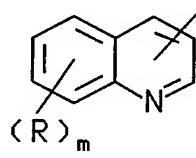
15 (7) when Q^1 is  and R^{102} is hydrogen, R^{101} cannot be alkylphenyl having

15

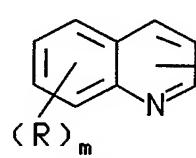
1 to 4 carbons in the alkyl portion and optionally substituted at the phenyl portion;

20

(8) when Q^1 is  and R^{101} is hydrogen, R^{102} cannot be (v), (w) or (y);



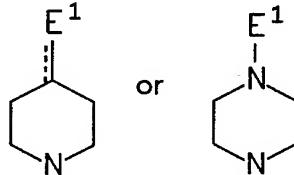
25

(9) when Q^1 is  , R^{101} and R^{102} taken together with the nitrogen to

25

30

which they are attached cannot be



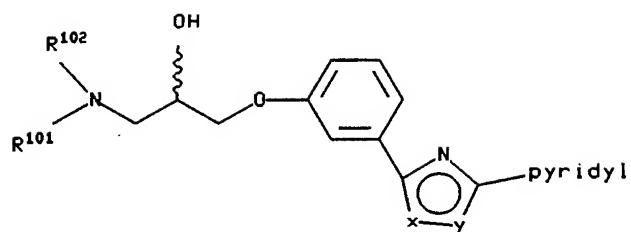
wherein E^1 is (nn) or (oo);

(10) when the compound of formula (I) is

35

-14-

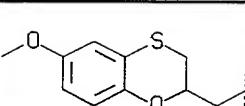
5



10 wherein X is N and Y is O or X is O and Y is N then R¹⁰¹ and R¹⁰² taken separately or together with the nitrogen to which they are attached cannot be the following:

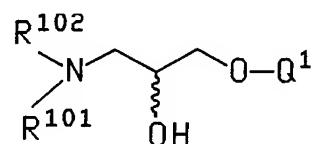
	R ¹⁰¹	R ¹⁰²	R ¹⁰¹ and R ¹⁰² taken together with the N to which they are attached
15	a	-	
20	b	-	
25	c	H	
30	d	H	
35	e	H	
	f	H	
	g	H	

-15-

	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
5	h n-butyl		

(11) when the compound of formula (I) is

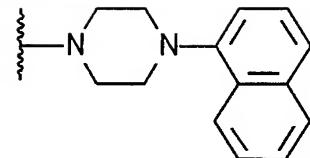
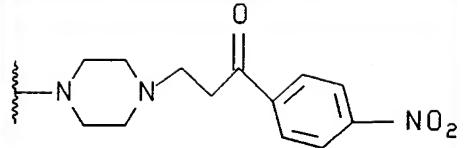
10



15

wherein Q^1 is quinolin-5-yl or 2-methylbenzthiazol-7-yl, then R^{101} and R^{102} taken separately or together with the nitrogen to which they are attached cannot be the following:

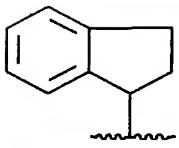
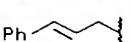
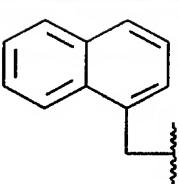
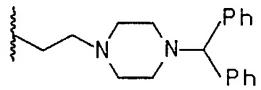
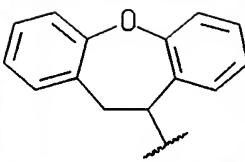
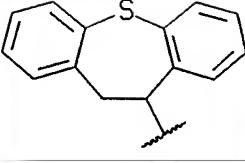
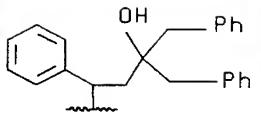
20

	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
25	a -	-	
30	b -	-	

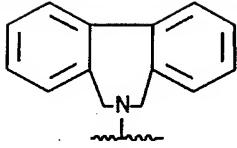
-16-

	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
5	c	-	-
10	d	-	
15			
20	e	H	
25	f	H	
30			

-17-

	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
5	g H		
10	h 		
15	i H		
20	j H		
25	k H		
30	l H		

-18-

	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
5	m	-	
10			

(12) when R^{102} is (u), and A^2 is a covalent bond, Z^3 cannot be hydroxy;

(13) when R^{101} and R^{102} are taken together with the nitrogen to which they are attached and forms (mm) and b is 1, J^1 cannot be nitrogen;

15 (14) the compound of the formula (I) is not methyl-[3-(2-methyl-benzothiazol-7-yloxy)-propyl]-naphthalen-1-ylmethyl-amine;

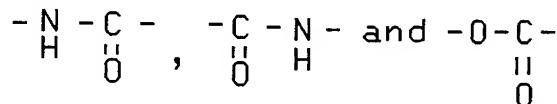
(15) the compound of the formula (I) is not 1-(4-diethylamino-2-methyl-benzothiazol-7-yloxy)-3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-propan-2-ol;

20 (16) the compound of the formula (I) is not 1-(6-allyl-2-methyl-benzothiazol-7-yloxy)-3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-propan-2-ol; and

25 (17) the compound of the formula (I) is not 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(6-methoxy-2-phenyl-benzothiazol-7-yloxy)-propan-2-ol.

It will be apparent to one skilled in the art that when Q^1 is (g), (h), (i), (j) or (k), Q^1 can be bonded to A^1 at any chemically available site on the molecule, and R can be bonded to any available site on the molecule.

For the partial structures



it is understood that they are inserted into the molecules in the specific orientation as drawn.

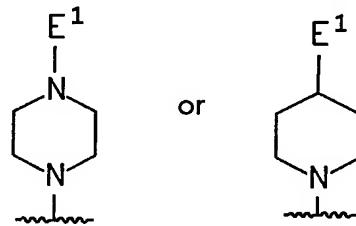
-19-

5 A preferred group of compounds is that group of compounds of formula I, above, wherein B¹ is an optionally substituted phenyl; Y² is attached to B¹ in an ortho or meta position relative to A¹-Q¹; A¹ is a covalent bond, O, S or -CH₂-; Q¹ is (a), (b), (c) or (d) wherein R, m and X¹ are as defined above; Y¹ is -CH₂-; Z¹ is hydrogen or hydroxy; n is 1 or 2; and Y² is O, NH, NCH₃ or S.

10 Another group of preferred compounds is that group of compounds of formula I, above, wherein B¹ is a covalent bond; Y¹ is O and Z¹ is hydrogen; or Y¹ is -CH₂- and Z¹ is hydrogen or hydroxy; n is 1 or 2; Y² is O, NH, NMe or S; and Q¹ is (g) wherein X² 15 is N, X³ is CR or N, and X⁴ is S or O; or X² is N, X³ is S or NR, and X⁴ is N; or X² is N, X³ is N or CR and X⁴ is NH or NMe.

15 A more preferred group of compounds is that group of compounds of formula I, above, wherein B¹ is an optionally substituted phenyl; Y² is attached to B¹ in the meta position relative to A¹-Q¹; A¹ is a covalent bond, O, S or -CH₂-; Q¹ is (c) wherein m is 20 1 and R is pyridin-3-yl or pyridin-4-yl; and R¹⁰¹ and R¹⁰² are taken together with the

nitrogen to which they are attached and form



wherein E¹ is (nn), (oo), (pp), or (qq) wherein X¹³, B⁵, r, X⁹, B³, G¹, G², J², X¹⁴, e, p and G³ are as defined above.

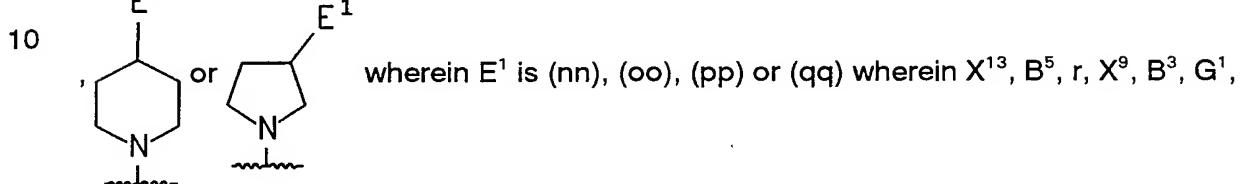
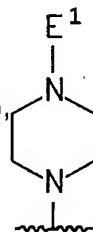
25 Another group of more preferred compounds is that group of compounds of formula I, above, wherein B¹ is an optionally substituted phenyl; Y² is attached to B¹ in the meta position relative to A¹-Q¹; n is 1; Y¹ is O; Z¹ is OH; A¹ is a covalent bond, O, S or -CH₂-; Q¹ is (c) wherein m is 1 and R is pyridin-3-yl or pyridin-4-yl; R¹⁰¹ is 30 hydrogen, alkenylphenyl having 2 to 4 carbons in the alkenyl portion or alkylphenyl having 1 to 4 carbons as defined above; and R¹⁰² is (p), (s), (u), (v) or (w) wherein X⁸, a, b, X⁹, A³, A⁴, B³, Z², r, Z⁴, B², A², Z³ and g are as defined above.

35 Yet another group of more preferred compounds is that group of compounds of formula I, above, wherein B¹ is a covalent bond; Y¹ is -CH₂-; Z¹ is OH; n is 1; Y² is O; Q¹ is (g) wherein X² is N, X³ is CR or N, and X⁴ is S or O; or X² is N, X³ is S or NR, and X⁴ is N; or X² is N, X³ is N or CR and X⁴ is NH or NMe; and R¹⁰¹ and R¹⁰²

-20-

are taken together with the nitrogen to which they are attached and is (bb), (ee), (ff),

5



15 G², J², X¹⁴, e, p and G³ are as defined above; or R¹⁰¹ is as defined above for formula I and R¹⁰² is (l), (n), (o), (p), (s), (u), or (x) wherein X⁹, r, X¹¹, Z², X⁸, a, b, Z³, Z⁴, B², A², X¹² and Y³ are as defined above.

Particularly preferred compounds of this invention are:

1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(3-methyl-3H-20 benzimidazol-4-yloxy)-propan-2-ol,

1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(3-methyl-3H-benzotriazol-4-yloxy)-propan-2-ol,

1-(benzothiazol-7-yloxy)-3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-propan-2-ol,

25 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

1-(4-benzhydryl-piperidin-1-yl)-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-dimethylamino-benzothiazol-7-yloxy)-propan-2-ol,

30 7-{3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-benzothiazole-2-carboxylic acid amide,

1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-pyridin-3-yl-benzothiazol-7-yloxy)-propan-2-ol,

1-(4-benzhydryl-piperidin-1-yl)-3-(2-pyridin-2-yl-benzothiazol-7-yloxy)-propan-2-ol,

35

-21-

1-(2-methyl-benzothiazol-7-yloxy)-3-[4-(2-propylsulfanyl-phenyl)-piperazin-1-yl]-propan-2-ol,

5 N-[1-(3-{4-[2-hydroxy-3-(2-methyl-benzothiazol-7-yloxy)-propyl]-piperazin-1-yl}-propyl)-1H-benzoimidazol-2-yl]-4-methoxy-benzamide,

1-(5-chloro-tricyclo[7.3.1.0,2,7]trideca-2,4,6,10-tetraen-13-ylamino)-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

10 3-[2-hydroxy-3-(2-methyl-benzothiazol-7-yloxy)-propylamino]-2-phenyl-decahydro-naphthalen-2-ol,

1-(4-benzhydryl-piperazin-1-yl)-3-[3-(5-pyridin-3-yl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol,

1-(4-benzhydryl-piperidin-1-yl)-3-[3-(5-pyridin-3-yl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol,

15 1-(4-benzhydryl-piperidin-1-yl)-3-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol,

1-(4-benzhydryl-piperidin-1-yl)-3-[3-(3-pyridin-3-yl-[1,2,4]oxadiazol-5-yl)-phenoxy]-propan-2-ol,

20 1-(methyl-naphthalen-1-ylmethyl-amino)-3-[3-(3-pyridin-3-yl-[1,2,4]oxadiazol-5-yl)-phenoxy]-propan-2-ol, and the pharmaceutically acceptable salts thereof.

25 A more particularly preferred group of compounds of this invention is:

1-[4-(2-chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

25 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-dimethylamino-benzothiazol-7-yloxy)-propan-2-ol,

7-{3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-2-hydroxy-propoxy}-benzothiazole-2-carboxylic acid amide,

30 1-{4-[2-hydroxy-3-(2-methyl-benzothiazol-7-yloxy)-propyl]-piperazin-1-yl}-2,2-diphenylethanone,

1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-pyridin-4-yl-benzothiazol-7-yloxy)-propan-2-ol,

35 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-isopropyl-benzothiazol-7-yloxy)-propan-2-ol,

1-(2-butyl-benzothiazol-7-yloxy)-3-(1-phenyl-cyclohexylamino)-propan-2-ol,

-22-

1-(2-butyl-benzothiazol-7-yloxy)-3-[1-(4-chloro-phenyl)-cyclohexylamino]-propan-2-ol,
1-(4-benzhydryl-piperidin-1-yl)-3-[3-(5-pyridin-3-yl-[1,2,4]oxadiazol-3-yl)-phenoxy]-
propan-2-ol,
5 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(3-methyl-3H-
benzoimidazol-4-yloxy)-propan-2-ol,
1-(4-benzhydryl-piperidin-1-yl)-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,
3-[2-hydroxy-3-(2-methyl-benzothiazol-7-yloxy)-propylamino]-2-phenyl-decahydro-
naphthalen-2-ol and the pharmaceutically acceptable salts thereof.

10 The present invention also includes a method of inhibiting a P-glycoprotein in
a mammal in need of such treatment which comprises administering to said mammal
a P-glycoprotein inhibiting amount of a compound of formula I. Preferred is the method
where the mammal is a human suffering from cancer and said compound is
administered before, with or after the administration to said human of an anticancer
15 effective amount of a chemotherapeutic agent.

Also included is a pharmaceutical composition for administration to a mammal
which comprises a P-glycoprotein inhibiting amount of a compound of formula I, a
pharmaceutically acceptable carrier or diluent and, optionally, an anticancer effective
amount of a chemotherapeutic agent.

20 As previously described, the compounds of formula I form pharmaceutically
acceptable acid addition salts. Said pharmaceutically acceptable acid addition salts
include, but are not limited to, those formed with HCl, HBr, HNO₃, H₂SO₄, H₃PO₄,
CH₃SO₃H, C₆H₅SO₃H, CH₃CO₂H, gluconic acid, lactic acid, 2-hydroxyethanesulfonic
acid, camphorsulfonic acid, tartaric acid, maleic acid and succinic acid. In the case of
25 those compounds of the formula I which contain a further basic nitrogens, it will, of
course, be possible to form higher acid addition salts (e.g., the dihydrochloride) as well
as the usual monoacid addition salt.

As one skilled in the art will recognize based upon the disclosure herein,
compounds of formula I have the potential for containing asymmetric carbon atoms.

30 All isomers of the compounds of formula I and the salts thereof are considered within
the scope of the present invention.

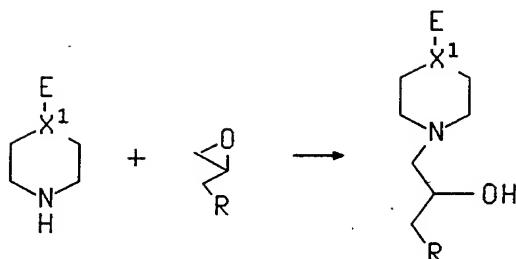
Detailed Description

35 The compounds of the invention can be prepared by a number of different
processes according to the invention. The following methods describe the synthetic
procedures which are employed to make the compounds of this invention.

-23-

METHOD A

5



10

(Oxiran-2-yl-methoxy)aromatic (1.0 equivalent (eq.)) in ethanol (EtOH), 2-propanol, EtOH/DMF or H₂O/dioxane (1:4) and the required amine (1.0-2.0 eq as free base) are mixed and heated to reflux (or in sealed tube at about 80-100°C) for several hours under N₂(g) until all of the epoxide has been consumed. The mixture is poured 15 into H₂O and extracted with ethyl acetate (EtOAc)/diethylether (Et₂O) (1:1 to 0:1). The organic phase is dried over MgSO₄ or Na₂SO₄, filtered and concentrated in vacuo. The residue is chromatographed on silica to yield the free base which is converted to a mono- or di-hydrochloride salt by treatment with the appropriate amount of 1.0M HCl in Et₂O or CHCl₃/Et₂O followed by either filtration of the precipitated salt and 20 recrystallization or by concentration in vacuo and recrystallization of the residue.

METHOD B

Reactions of glycidyl ethers with amine salts are carried out as described in Method A but with the addition of 1.0-2.5 eq. of diisopropylethylamine to the reaction mixture.

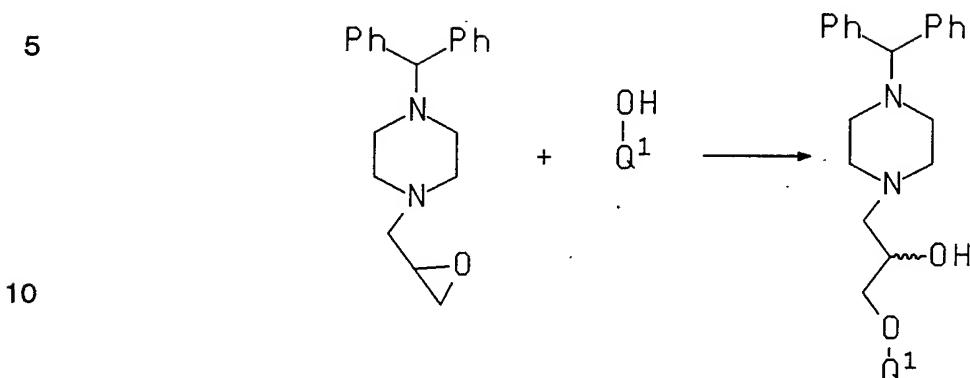
25

30

35

-24-

METHODS C_A, C_B and C_C



METHOD C_A

15 To a solution of a glycidylamine (specifically, 1-benzhydryl-4-oxiran-2-ylmethyl-piperazine; 1.0-2.0 mol eq.) and phenol (1.0 mol eq.) in 2-propanol or n-butanol is added aqueous KOH or NaOH (1.0 mol eq. of 1-6*N*). The stirred mixture is refluxed under N₂(g) atmosphere for 5-48 hours. The reaction is concentrated in vacuo and the residue is flash chromatographed on silica (EtOAc/hexanes or acetone/hexanes) to afford the product as the free base.

METHOD C_R

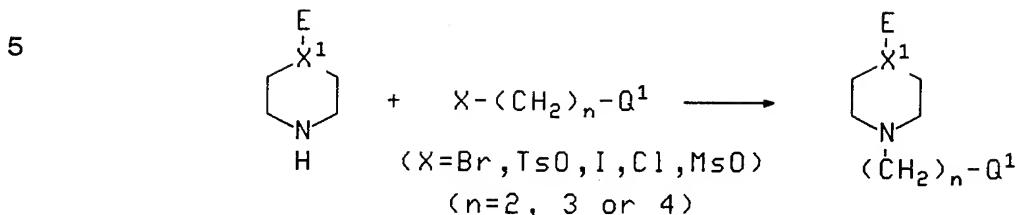
The method of C_A, above, is employed except (1.0 mol eq.) K₂CO₃(s) is utilized in refluxing n-BuOH (5-16 hours) rather than aqueous KOH or NaOH.

METHOD C₆

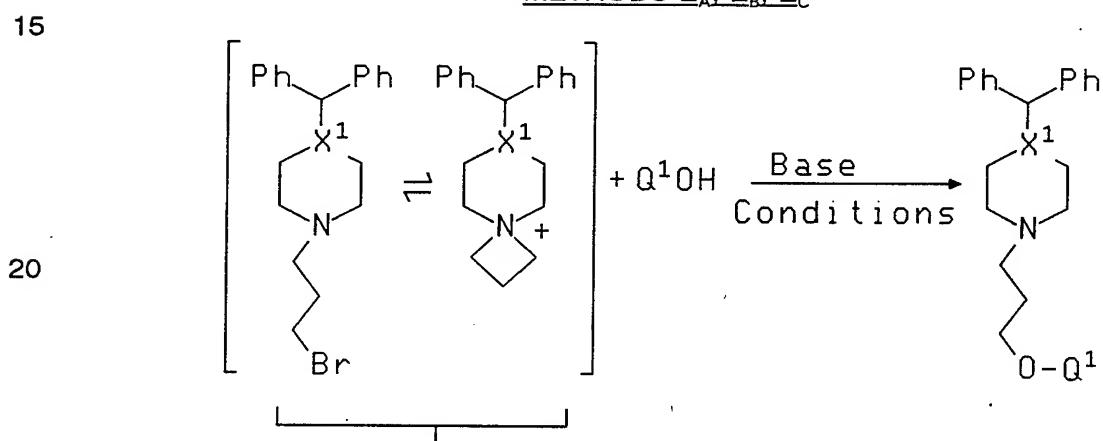
25 To phenol (1 mmol) in anhydrous DMF (1.5 mL) is added a catalytic amount of NaH (0.1-0.2 eq.). After evolution of $H_2(g)$ has ceased, the glycidylamine (1 mmol) is added and the mixture is stirred at about 50°C for 24-72 hours under $N_2(g)$. The reaction mixture is poured into H_2O , the pH adjusted to 12-14 with 1N NaOH, and the product is extracted into 1:1 EtOAc/Et₂O. The organic extracts are combined, dried over Na₂SO₄, concentrated in vacuo and flash chromatographed to obtain the product as its free base.

30

-25-

METHOD D

10 To a haloalkyl aryl ether (1.0 eq.) in *t*-BuOH is added the appropriate amine (1-5 eq.). The mixture is stirred at about 40-80°C for about 2-36 hours until most of the aryl ether is consumed. Solvent is removed *in vacuo* and the residue is chromatographed on silica to obtain the product as its free base.

METHODS E_A, E_B, E_CMETHOD E_A

A hydroxyaromatic (1.0 eq.) is dissolved in dry DMF (2.8 mL) and $\text{Me}_4\text{N}^+\text{OH}^- \cdot 5\text{H}_2\text{O}$ (0.95 eq.) is added with stirring under $\text{N}_2(\text{g})$. If an acid salt of the hydroxyaromatic is employed, 1.95 eq. of base are used. To the resulting solution of the phenolate is added the appropriate bromoalkylamine intermediate (0.5-1.0 eq.) and the mixture is stirred at about 40-100°C (typically 50-90°C) for about 2-48 hours until no further product formation (by HPLC detection methods) is evident. The mixture is partitioned between 1N NaOH and 1:1 EtOAc/Et₂O. The organic phase is washed with 1N NaOH (2x) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue

35

-26-

is chromatographed on silica (acetone/hexanes or MeOH/CH₂Cl₂) to afford the product as its free base.

METHOD E_B

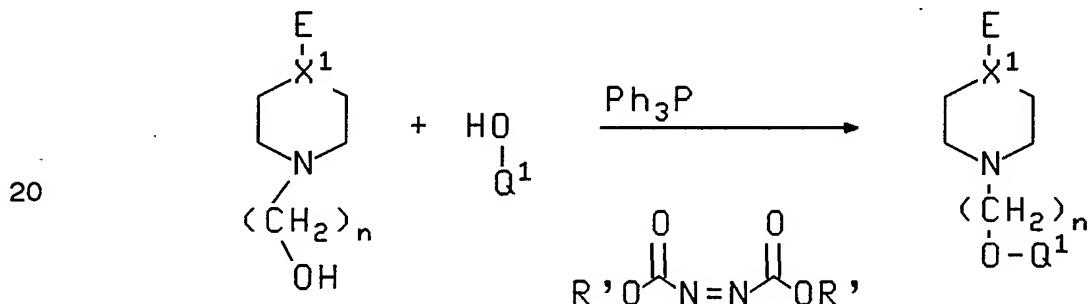
5 Method E_A above is employed but NaH is utilized in formation of the phenolate solution in DMF, often with subsequent addition of KI or n-Bu₄N⁺I⁻ as nucleophilic catalysts.

METHOD E_C

10 A hydroxyaromatic (1.25 mmol), n-Bu₄N⁺I⁻ (1.0 mmol, 369 mg) and an ω -bromoalkylamine intermediate (1.0 mmol) in CHCl₃ or CH₂Cl₂ (2-10 mL) are mixed and stirred vigorously with aqueous NaOH (0.5-4N; \geq 5 eq.) at about 20°C under N₂(g) for about 5-72 hours. Following addition of more solvent (\approx 25 mL), the organic phase is separated, washed with 0.5N NaOH and brine, concentrated in vacuo, and chromatographed on silica to recover the product as its free base.

15

METHOD F



25 To a partial suspension or solution of Ph₃P (1.2 eq.) and a hydroxyaromatic (1.0 eq.) in dry THF (7.0 mL) at about 0°C is added diethylazodicarboxylate (1.2 eq.) dropwise over several minutes. After 5 minutes at about 0°C a suspension of an amino alcohol [typically 1-benzhydryl-4-(3-hydroxypropyl)piperazine (1.0 eq.) in dry THF (5.0 mL + 2.0 mL rinse)] is added dropwise over 5 minutes to the solution. The reaction mixture is stirred for about 30 minutes at about 0°C and for about 16 hours at about 30 20°C, and then concentrated in vacuo. Products are isolated as their free base by chromatography on silica, or as their crude HCl salts by precipitation from EtOAc/Et₂O solution upon addition of 1M HCl in Et₂O (2.2 mL, 2.2 mmol) and cooling to about 4°C. When necessary crude, HCl salts are purified by recrystallization (e.g., from CHCl₃) or by free-basing, washing the organic phase with 1N NaOH and brine, and reprecipitating 35 the HCl salt from the organic extracts.

-27-

Method G_A

To the desired primary or secondary amine (1.0 mmol as its free base) in 20% H₂O/80% dioxane or THF (5mL) with 1-3 equivalents of Amberlite IRA-400® resin (OH form; 0.43-1.30 g of ≈ 2.3 meq/g, previously washed with MeOH and dried in vacuo) is added the appropriate (oxiran-2-yl-methoxy-heteroaromatic derivative, 0.6-1.0 mmol). The mixture is heated to about 50-85°C for about 4-60 hours under N₂(g) until no detectable epoxide remains (by TLC or analytical RP-HPLC). The resin is removed by filtration and the filtrate is concentrated in vacuo, redissolved in a small volume of 80% CH₃CN/2.0M pH 4.5 NH₄OAc buffer (2.5mL) and purified by preparative reversed-phase HPLC (typically by injection onto a Dynamax-60A C18 column (21.4 mm x 25 cm; 8μm packing) previously equilibrated in 15% CH₃CN/85% pH 4.5, 50 mM NH₄OAc followed by elution (20-25 mL/min) with a 1% CH₃CN/min. gradient). Products are recovered by lyophilization or concentration in vacuo at about 35-40°C and the residue is partitioned between saturated aqueous Na₂CO₃ and CHCl₃ or EtOAc. Organic fractions are dried over Na₂SO₄ (s) and concentrated in vacuo to afford the product as its free base. Conversion to the HCl salts typically involve dissolution of this residue in minimal CHCl₃, EtOAc or Et₂O, titration with the appropriate amount of 1M HCl in Et₂O (1-3 eq.), further dilution with Et₂O and cooling. Precipitated hydrochloride salts are filtered, washed with Et₂O and petroleum ether and dried in vacuo.

Method G_B

This method is conducted in essentially the same manner as described for Method G_A. However, amine salts (hydrochlorides, toluenesulfonates, maleates, etc.) are employed along with the appropriate number of neutralizing equivalents of aqueous NaOH in addition to the usual 1-3 equivalents of Amberlite IRA-400® resin (OH form).

Method H

A suspension of NaH (60% oil dispersion, 1 eq) and the appropriate hydroxy compound (1 eq.) are mixed in a solvent such as tetrahydrofuran (THF) and warmed to about 50°C for about 30 minutes. A bromoalkylamine is added to the mixture and stirred at about 50°C for about 3 hours. The solvent is evaporated and the crude product is purified by silica gel chromatography to yield the desired product.

The following is the preferred method of forming the salt of a compound of formula I. For monohydrochlorides, the purified free base was dissolved at about 20°C in a minimum volume of CHCl₃ or EtOAc (or Et₂O if sufficiently soluble) and diluted with dry Et₂O, usually to the point where further addition would cause permanent cloudiness.

-28-

A solution of 1.0M HCl in dry Et₂O (1.05 eq) is added dropwise with stirring causing precipitation of the monohydrochloride salt which is recovered, after cooling to about 0°C, by centrifugation or filtration, washed with Et₂O and pet. ether and dried in vacuo 5 to constant mass. For di- and trihydrochloride salts, the free base was dissolved in minimal alcohol (MeOH or EtOH) or acetonitrile and the solution was treated dropwise while stirring with the appropriate volume of 1.0M HCl in Et₂O (ideally maintaining most material in solution until the addition of the final equivalent of acid has begun by 10 additions of alcohol or CH₃CN as required). When the addition is complete, the salt may be precipitated by dilution with dry Et₂O and cooling, or by concentration in vacuo 15 and either trituration with Et₂O or recrystallization from alcohol/Et₂O or CH₃CN/Et₂O. Precipitated salts are recovered by centrifugation or filtration, and washed with Et₂O and pet. ether and dried in vacuo to constant mass.

The following procedures are utilized to synthesize the starting materials for the 15 compounds of this invention.

METHOD I

Preparation of Glycidyl Ethers (Oxiranyl-2-Methoxy-aromatics)

NaH (1.1 eq.) is added to a solution of the appropriate phenol (1.0 eq., 1M) in anhydrous DMF. The mixture is stirred at about 40°C under N₂(g) until the evolution 20 of H₂(g) ceases. Epibromohydrin (1.10 eq.) is added and the mixture is stirred at about 60°C for about 0.5 to 16 hours until the reaction is complete by TLC/HPLC. The mixture is poured onto ice/H₂O and extracted with Et₂O or 1:1 EtOAc/Et₂O. Organic extracts are pooled, washed with H₂O and saturated NaCl(aq), dried over Na₂SO₄(s) 25 and concentrated in vacuo. The product could be purified by chromatography on silica gel or utilized directly in reactions with amines.

METHOD II

(2R)- and (2S)-glycidyl ethers are prepared from the corresponding (2R)- and (2S)-glycidyl-3-nitrobenzenesulfonates at about 30-45°C (or *p*-toluenesulfonates at about 40-60°C), respectively, instead of epibromohydrin, according to the procedure 30 of Method I, above.

METHOD III

Alternate Preparation of Glycidyl Amines

To a solution of a secondary amine, typically 1-benzhydrylpiperazine (10.0 g, 39.6 mmol), in dioxane (80-110 mL) is added a tertiary amine (39.6 mmol; e.g., 35 diisopropyl ethyl amine or N-methyl morpholine) followed by epibromohydrin (119

-29-

mmol, 16.3 g). The mixture is stirred at about 22°C for about 16 hours, and precipitated salts are removed by filtration. The filtrate is concentrated in vacuo, redissolved in EtOAc (150 mL), washed with 1.0N NaOH (2 x 50 mL) and brine (50 mL),
5 dried over Na₂SO₄(s) and then flash chromatographed on silica (40% acetone/hexanes) to afford pure glycidyl amine.

METHOD IV

Preparation of Haloalkyl Aryl Ethers

To the appropriate hydroxyaromatic (20 mmol) in anhydrous DMF or THF (45 mL) is added NaH (20 mmol, 1.0 eq.). After evolution of H₂(g) ceases and all of the NaH(s) has dissolved (with gentle warming if required) an excess (100-200 mmol, 5-10 eq.) of 1,2-dibromoethane (for n=2), 1,3-dibromopropane (n=3), 1,4-dibromobutane (n=4), alkylchlorides, alkyl iodides, tosylates or triflates is added. Stirring under N₂(g) is continued at about 20-60°C for about 2-24 hours until almost all of the phenol is
10 consumed. The mixture is poured into 5% aq. Na₂CO₃ and extracted (CHCl₃, EtOAc or Et₂O). The pooled organic extracts are washed with 10% Na₂CO₃ and brine, dried over Na₂SO₄(s), concentrated in vacuo and the product isolated by chromatography on
15 silica (acetone/hexanes or EtOAc/hexanes). When the aryl moiety is sufficiently basic (pKa 2.5-8) the ether product can often be isolated by precipitation of its HCl salt from
20 Et₂O or EtOAc.

METHOD V

Method IV, above, is employed but (1 eq.) tetraalkylammonium hydroxide salt (typically Me₄N⁺OH⁻·5H₂O) is used as a base instead of NaH.

METHOD VI

25 To a stirred slurry of the appropriate hydroxyaromatic (10 mmol) and Ph₃P (12 mmol, 1.2 eq.) at about -20°C to 0°C in anhydrous THF (20 mL) is added diethyl azodicarboxylate (12 mmol, 1.2 eq.) dropwise, immediately followed by 2-bromoethanol (for n=2) or 3-bromopropanol (n=3) (12 mmol, 1.2 eq.) dropwise. The stirred mixture is allowed to warm to about 20°C for about 16 hours. Solvent is removed in vacuo and
30 the residue is chromatographed on silica (EtOAc/hexanes or acetone/hexanes) to afford the bromoalkylether (typically 70-98% yield).

METHOD VII

Preparation of 1-Benzhydryl-4-(3-bromopropyl)piperazine

1,3-Dibromopropane (5 eq., 199 mmol, 20.3 mL) is added to a stirred solution
35 of 1-benzylhydrylpiperazine (10.1 g, 40 mmol) under one of the sets of reaction

-30-

conditions listed below. The mixture is stirred until thin layer chromatography TLC (35% acetone/hexanes) indicates detectable amounts of slower moving 1,3-bis(1-benzyhydryl-piperazinyl)propane dialklylation by-product have been produced in addition to the 5 initial desired product. The reaction mixture is partitioned between CH_2Cl_2 or CHCl_3 and saturated aqueous NaHCO_3 . The organic phase is washed with saturated NaHCO_3 , dried over $\text{Na}_2\text{SO}_4(s)$ and concentrated in vacuo to a yellow oil which is immediately flash chromatographed on silica in 15% acetone/hexanes. When necessary, recovered product is triturated with heptanes to remove residual 10 dibromopropane and yield the product as a white solid consisting of a dynamic mixture of the desired bromopropyl derivative and its corresponding cyclized azetidinium bromide salt.

Reaction Conditions:

- A. Dioxane (50-80 mL), room temperature, \approx 3 hours.
- 15 B. 80% Dioxane or i-PrOH (50-80 mL)/20% H_2O , 2 eq. Na_2CO_3 , room temperature, \approx 5 hours.
- C. CH_2Cl_2 (\approx 100 mL), 1.1 eq., $\text{K}_2\text{CO}_3(s)$, about 5°C, 1 hour.

METHOD VIII

Preparation of 4-Benzhydryl-1-(3-hydroxypropyl)piperidine

20 4-Benzhydrylpiperidine (10 mmol, 2.87 g) is slurried in n-butanol (30 mL), and $\text{K}_2\text{CO}_3(s)$ (2.76 g, 10 mmol) or diisopropylethylamine (20 mmol, 2.5 g) and 3-bromopropanol (10 mmol, 1.39 g) are added to the slurry. The stirred mixture is refluxed for about 7 hours under $\text{N}_2(g)$, filtered, and concentrated in vacuo. The residue is dissolved in hot CHCl_3 , filtered and concentrated in vacuo to yield crude product as 25 an oil (3.0-3.1 g) which is used without further purification.

METHOD IX

Preparation of 4-Benzhydryl-1-(3-chloropropyl)piperidine

Crude hydroxypropyl piperidine from above (3.1 g, \leq 10 mmol) in anhydrous CHCl_3 or CH_2Cl_2 (30 mL) is treated with thionyl chloride (10 mmol) and the mixture is 30 refluxed for about 2 hours under dry $\text{N}_2(g)$. The residue after evaporation in vacuo is chromatographed on silica (10% MeOH in CH_2Cl_2) to yield 1.6 g of product as a white solid.

METHOD X

Preparation of 1-Benzhydryl-4-(3-hydroxypropyl)piperazine

-31-

To 1-benzhydrylpiperazine (64 mmol) and diisopropylethylamine (77 mmol) in dioxane/H₂O (9:1, 100 mL) is added 3-bromo-1-propanol (64 mmol) while stirring. After about 17 hours, the solution is concentrated in vacuo, and the residue is taken up in EtOAc (250 mL) and washed with 1N NaOH (2 x 100 mL), and brine (2x). The organic 5 phase is dried over Na₂SO₄(s), concentrated in vacuo and recrystallized from hot EtOAc to afford white crystalline product.

Compounds of formula I are inhibitors of the functions of P-glycoprotein, particularly human *MDR1* protein or P-glycoprotein related and membrane associated proteins which participate in the transport of xenobiotics or proteins across membranes 10 such as, cell membranes of eukariotic and prokariotic origin, e.g., pmfdr, however not exclusive or restricted to these examples.

Compounds included in general formula I are useful in combination chemotherapy of cancer, malaria, viral infections such as AIDS, in therapy of septic shock syndrome or inflammation and may be useful in enhancing of the xenobiotics 15 limited due to the presence of P-glycoprotein or P-glycoprotein related functional proteins. Compounds of formula I increase the activity/efficacy of adriamycin, daunomycin, etoposide, topotecan, teniposide, actinomycin D, taxol, vincristine, vinblastine, anthracycline antibiotics and of drugs which are structurally and functionally related to the above mentioned examples. In particular, compounds of formula I are 20 useful when the activity of such drugs has been shown to be limited due to the presence and function of P-glycoprotein, e.g. human *MDR1* protein or P-glycoprotein related proteins.

The effectiveness of the compounds of the present invention in sensitizing multidrug resistant KBV-1 cells to adriamycin (ADR) (Aria Labs) were sometimes 25 identified using an assay which determined the degree of potentiation of adriamycin's cytotoxicity effects by the compounds. Plates inoculated with 5 x 10³ cells in 200 μ L RPMI 1640 (J.R.H. Bioscience) supplemented with 10% fetal bovine serum albumin plus penicillin (100 units/mL) and streptomycin (100 μ g/mL) were incubated 1 day at 37°C, 30 5% CO₂ and 98% humidity. RPMI media (25 μ L) containing 50 μ M adriamycin was added to each plate (5 μ M ADR final). Compounds (30 mM) were solubilized in DMSO and diluted with 1 mM Tris buffer, pH 7.4, and 25 μ L aliquots of appropriately diluted solutions were added to test plates of cells (in triplicate) to produce final concentrations of 15 μ M to 15 nM compound per plate. Control plates were treated with 25 μ L of the appropriate DMSO/Tris buffer "blank" solutions for comparison. All plates were 35

-32-

incubated at 37°C, 5% CO₂, 98% humidity for 66 h. before adding 25 μ L of MTT (2.5 mg/mL) (3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, Sigma) and incubating for 3 h. Media was aspirated and DMSO (100 μ L) was added to each plate.

5 Plates were placed on a shaking platform for 30-60 min. to dissolve the dye and then the optical density was determined at 570 nm as a relative measure of cell viability.

The compounds of the present invention are evaluated as potentiators of chemotherapeutic agents using a Cellular Drug Retention Assay. This assay was designed to study the effect of compounds on cellular retention of radiolabeled drug.

10 In this case ¹⁴C-adriamycin retention by multidrug resistant human carcinoma cells, KBV1, is measured. The KBV1 cell line was obtained from M. Gottesman and I. Pastan of the National Cancer Institute, Bethesda, Maryland, 20892, U.S.A.

15 KBV1 cells are routinely grown in tissue culture as monolayers in DMEM high glucose medium containing 1 μ g/ml vinblastine, 10% heat inactivated fetal calf serum and supplemented with glutamine, pen-strep and garamycin.

The assay protocol (described below) is applicable with minor modifications, to a wide variety of cell lines grown in tissue culture.

Assay Protocol:

(1) Seed replicate 6-well tissue culture plates with 1.2x10⁶ cells per 2 ml per well 20 in absence of vinblastine;

(2) Incubate 24 hours at 37°C in humidified incubator (5% CO₂);

(3) Aspirate off the spent media and overlay monolayers with 2 ml/well of fresh medium that contains 2 μ M adriamycin (2 μ M unlabeled adriamycin + 20,000 cpm of ¹⁴C-adriamycin) and the test compound at concentrations varying from 0 to 100 μ M;

25 (4) Following incubation for 3 hours at 37°C in humidified incubator, remove media and wash monolayers twice with 2 ml of ice cold buffered saline;

(5) Detach monolayers using 0.5 ml of trypsin/EDTA, collect detached cells and transfer to scintillation vial. Rinse wells once with 0.5 ml of buffered saline and add to same vial containing cells;

30 (6) Add 5 ml of Beckman Ready-Safe™ scintillation fluid to vial, vortex and determine radioactivity per sample using a scintillation counter (10 minutes per sample);

(7) For background control: pre-incubate monolayers at 4°C for 15 minutes then remove media and add fresh ice-cold media containing adriamycin (see step 3).

Following incubation for 3 hours at 4°C remove media and wash monolayers twice with 2 ml ice-cold buffered saline, then proceed as in step 5;

-33-

(8) Results are expressed as T/C and ED3x values as defined below:

T/C = pmoles adriamycin per 10^6 cells treated with test compound/concentration

5 ED3x = concentration of test compound that produces a 3 fold increase in cellular accumulation of radiolabeled adriamycin, i.e. T/C = 3.

Calculation

Specific cpm = [sample cpm - background cpm]

Specific activity = [cpm/total conc. of adriamycin]

10 pmoles adriamycin = [specific cpm/specific activity]

pmoles adriamycin per 10^6 cells = [(pmoles adriamycin per well/number of cells per well) $\times 10^6$ cells]

15 As previously mentioned, compounds of the present invention and salts thereof are useful in potentiating the anticancer effects of chemotherapeutic agents. Such agents can include adriamycin, daunomycin, topotecan, teniposide, actinomycin D, vinblastine, vincristine, etoposide, mitomycin C and anthramycin.

20 The compounds of the present invention can be administered with, 24 hours before or up to 72 hours after the administration of the chemotherapeutic agents. When administered with said agents, they can be taken either separately or coadministered in the same formulation.

25 The compounds of the present invention, whether taken separately or in combination with an anti-cancer agent, are generally administered in the form of pharmaceutical compositions comprising at least one of the compounds of formula I and optionally a chemotherapeutic agent, together with a pharmaceutically acceptable vehicle or diluent. Such compositions are generally formulated in a conventional manner utilizing solid or liquid vehicles or diluents as appropriate to the mode of desired administration such as oral, buccal, transdermal, parenteral, rectal or slow infusion. For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. sodium lauryl sulphate or sodium starch glycolate). The tablets may be coated by methods well known in the art. Liquid 30 preparations for oral administration may take the form of, for example, solutions, syrups 35

-34-

or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending

5 agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

10 Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

15 The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily, aqueous or alcoholic vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active 20 ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

25 For use in the potentiation of anticancer agents in a mammal, including man, a compound of formula I is given in an amount of about 0.5-250 mg/kg/day, in single or divided doses. A more preferred dosage range is 2-50mg/kg/day, although in particular cases, at the discretion of the attending physician, doses outside the broader range may be required. The preferred route of administration is generally parenteral 30 either as a bolus injection or as a continuous infusion, but oral administration will be preferred in special cases. For compounds of this invention administered as a bolus intravenous injection the preferred dosage range is typically 0.1 - 5 mg/kg/day. When the compounds of this invention are administered as a continuous intravenous infusion, a 0.1 - 5 mg/kg loading dose is given as an i.v. bolus injection followed by a 35 maintenance slow infusion of 0.1 - 2 mg/h/kg (depending on the targeted plasma level

-35-

and the individual's clearance rate) begun 1 hour before and continuing for at least 3 hours following dosing of a chemotherapeuticant is preferred. When a compound of this invention is administered orally, the preferred dosage range is 0.5 - 50 mg/kg/day. The 5 maximal doses of the compounds of this invention is determined by the toleration of the combination of a compound of this invention and a particular cytotoxic agent by the patient.

The present invention is illustrated by the following examples, but is not limited to the details or scope thereof.

10 Amberlite IRA 400 (OH) ion exchange resin was purchased from Aldrich Chemical Co., Inc (Milwaukee, WI, 53233) and washed thoroughly with 80% dioxane/H₂O and MeOH and dried before use in reactions.

15 Analytical reverse phase (RP) HPLC is carried out by injecting samples, dissolved in a solvent miscible with water, onto a Perkin Elmer Pecosphere column (C₁₈, 3mm x 3 cm, available from Perkin Elmer Corp. Norwalk, CT. 06859) with a Brownlee RP-8 Newguard precolumn (7 micron, 15 mm x 3.2 mm, available from Applied Biosystems Inc., San Jose, CA. 95134). The samples are eluted with a linear gradient of 0 to 100% acetonitrile/pH 4.55, 200 mM NH₄OAc buffer over 10 minutes, at 3.0 mL/minute. UV detection is typically at 240-310nm depending on the λ_{max} of the 20 heterocycle in the sample.

25 Preparative reverse phase (RP) HPLC is performed using a Dynamax-60A C18 (8 μ m) column (21.4 mm x 25 cm) equipped with a Guard Module (21.4 mm x 25 cm), both available from Rainin Instrument Co. Reaction mixture residues are taken up in CH₃CN/H₂O or MeOH/H₂O at pH 4-5 and injected onto the column which had previously been washed and equilibrated in 0 to 15% CH₃CN/pH 4.5 50 mM NH₄OAc buffer. Elution of components is carried out with a linear gradient of 1% CH₃CN/minute at 20-25 mL/min. flow rates with detection at 260-310 nm as appropriate for heterocyclic fragments.

30

35

-36-

Example 1

(Method A)

1-[4-(10, 11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl]-3-(2-methyl-5
benzothiazol-7-yloxy)propan-2-ol hydrochloride

2-Methyl-7-(oxiran-2-ylmethoxy)benzothiazole (0.79 mmol, 174 mg) and 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine were stirred at reflux about 80°C in 20% DMF/80% EtOH (5mL) for 3 hours. The residue after concentration in vacuo was flash chromatographed on silica in 35% acetone/hexanes to afford 204 mg of product as its free base (52%). This material was dissolved in Et₂O and 1N-HCl in Et₂O (1.0 eq, 0.41 mL) was added dropwise with stirring under dry N₂(g). After 30 min, the suspension was chilled, and the white precipitate was recovered by centrifugation (with 2x washes of pellet with anhydrous Et₂O) and dried in vacuo to yield 190 mg (86% recovery) of the hydrochloride salt. LSIMS m/z 500 (MH⁺ of C₃₀H₃₃N₃O₂S); mp 153.5°C.

15

Example 2

(Method A)

1-(4-Benzhydryl-piperazin-1-yl)-3-(2-benzothiazol-2-yl-phenoxy)propan-2-ol

A solution of 1-benzhydryl-piperazine (891 mg, 3.53 mmol) and 2-[2-(oxiran-2-ylmethoxy)phenyl]benzothiazole (1000 mg, 3.53 mmol) in EtOH (7 mL) were refluxed under N₂(g) for about 16 hours. The mixture was concentrated in vacuo to a white foam and flash chromatographed on silica (35% EtOAc/hexanes) to afford 807 mg (42%) of the free base of the product as a white solid. mp 152-155°C; LSIMS m/z 536 (MH⁺).

25

Example 3

(Method B)

1-(4-Benzhydryl-piperidin-1-yl)-3-(2-pyridin-2-yl-benzothiazol-5-yloxy)propan-2-ol

4-Benzhydrylpiperidine (1.63 mmol, 0.47 g) and 5-(oxiran-2-ylmethoxy)-2-pyridin-2-yl-benzothiazole (1.62 mmol, 0.46 g) were stirred at reflux (about 80°C) under N₂(g) in 20% DMF/80% EtOH (5 mL) for 16 hours. The mixture was concentrated in vacuo and the residue was flash chromatographed on silica using 35% acetone/65% hexanes to afford 340 mg of product as its free base (39%; white powder). This material was dissolved in a minimal amount of CHCl₃ and 1N HCl in Et₂O (1.1 eq, 0.70 mL) was added dropwise with stirring. After about 30 min. the mixture was concentrated in vacuo and the residual white solid was triturated with Et₂O, filtered and dried in vacuo

35

-37-

to yield 337 mg (92% recovery) of the product as its monohydrochloride salt. LSIMS m/z 535 (MH⁺ of C₃₃H₃₃N₃O₂S); mp 165-172°C.

Example 4

5

(Method C_A)

1-(4-Benzhydryl-piperazin-1-yl)-3-(2-benzoxazol-2-yl-phenoxy)propan-2-ol

To 2-(benzoxazol-2-yl)phenol (342 mg, 1.62 mmol) dissolved in propan-2-ol (5 mL) was added 6 N KOH (0.8 mmol, 130 mL), diisopropylethyl amine (209 mg, 1.62 mmol), and 1-benzhydryl-4-(oxiran-2-ylmethyl)-piperazine (500 mg, 1.62 mmol). The reaction mixture was refluxed under N₂(g) for about 36 hours, then concentrated in vacuo and flash chromatographed on silica (20% acetone/hexanes) to afford 375 mg (49%) of the product as its free base. mp 140-143°C; LSIMS m/z 520(MH⁺).

Example 5

(Method C_B)

15

1-(4-Benzhydryl-piperazin-1-yl)-3-(3-[1,3,4]-thiadiazol-2-yl-phenoxy)propan-2-ol

To 1-benzhydryl-4-(oxiran-2-ylmethyl)-piperazine (617 mg, 2.0 mmol) and 3-([1,3,4]thiadiazol-2-yl)phenol (534 mg, 3.0 mmol) in n-BuOH (8 mL) was added K₂CO₃(s) (414 mg, 3.0 mmol). The stirred mixture was heated to reflux under N₂(g) for about 22 hours. The mixture was partitioned between 0.5N NaOH and 1:1 EtOAc/Et₂O. The organic phase was dried over Na₂SO₄(s), concentrated in vacuo and flash chromatographed on silica (25% acetone/hexanes) to yield 392 mg (40%) of the product as its free base. This material was dissolved in minimal CHCl₃ and treated dropwise with 1M HCl in Et₂O (0.85 mL, 0.85 mmol). After dilution to 20 mL with Et₂O and 30 min. stirring at about 20°C the monohydrochloride salt was recovered by filtration and dried in vacuo. 418 mg, 40%; mp 144-146°C; LSIMS m/z 487.

Example 6

(Method C_C)

1-(4-Benzhydryl-piperazin-1-yl)-3-(2-benzotriazol-2-yl-4-methyl-phenoxy)propan-2-ol

1-Benzhydryl-4-(oxiran-2-ylmethyl)-piperazine (300 mg, 0.97 mmol) was added 30 to the solution resulting from addition of catalytic NaH (5 mg of 60% dispersion in oil) to 2-(2'-hydroxy-5-methylphenyl)benzotriazole (219 mg, 0.97 mmol) in DMF (3 mL). The mixture was heated to about 50°C for about 72 hours under N₂(g), and then partitioned between 1N NaOH and 1:1 Et₂O/EtOAc. The organic phase was washed with 0.5N NaOH and brine, dried over Na₂SO₄(s) and concentrated in vacuo. The residue was 35 flash chromatographed on silica (20% acetone/hexanes) to afford 211 mg (41%) of

-38-

product as its free base. This material was converted to its monohydrochloride salt by precipitation from Et₂O on titration with 1M HCl in Et₂O (1.0 eq). mp 218-219°C; LSIMS m/z 534 (MH⁺).

5

Example 7

(Method D)

2-[2-[2-(4-Benzhydryl-piperazin-1-yl)-ethoxy]phenyl]-benzothiazole

1-Benzhydryl-piperazine (2.26 g, 8.98 mmol) and 2-[2-(2-bromoethoxy)phenyl]-benzothiazole (0.75 g, 2.24 mmol) were stirred in t-BuOH (20 mL) at about 50°C under 10 N₂(g) for 24 hours. The mixture was concentrated in vacuo and flash chromatographed on silica (15% acetone/hexanes) to afford 460 mg (41%) of the free base of the product. mp 67-72°C; LSIMS m/z 506 (MH⁺).

Example 8

(Method E_A)

15

6-[3[4-(Benzhydryl)piperazin-1-yl]propoxy]benzothiazole

6-Hydroxybenzothiazole (2.8 mmol, 423 mg) was dissolved in dry DMF (2.8 mL) by the addition of Me₄N⁺OH⁻.5H₂O (490 mg, 2.7 mmol) with stirring under N₂(g). 1-Benzhydryl-4-(3-bromopropyl)piperazine (716 mg, 2.0 mmol) was added to the solution and the mixture was stirred under N₂(g) at about 50°C for 16 hours. The reaction 20 mixture was partitioned between 1N NaOH (25 mL) and 1:1 EtOAc/Et₂O (25 mL). The organic phase was washed with 1N NaOH (2x10 mL), and brine(10 mL), dried over Na₂SO₄(s) and concentrated in vacuo. The residue was flash chromatographed on silica (25 to 35% acetone/hexanes) to afford 452 mg (51%) of the product as its free 25 base. This material was dissolved in a minimal amount of CHCl₃ at about 20°C, and 1M HCl in Et₂O (1.05 ml, 1.0 eq) was added dropwise with stirring. After the addition the suspension was diluted to ~20 ml with anhydrous Et₂O and the precipitated monohydrochloride salt was filtered and dried in vacuo; 403 mg, 42%. mp 136-137°C; LSIMS m/z 444 (MH⁺).

30

Example 9

(Method E_B)

1-Benzhydryl-4-[3-[2-(oxazol-2-yl)phenoxy]-propyl]piperazine

2-(Oxazol-2-yl)phenol (125 mg, 0.78 mmol) in dry DMF (2.0 ml) was treated with NaH (0.78 mmol; 32 mg of 60% dispersion in oil). After stirring 10 min. at about 20°C H₂(g) evolution had ceased and KI (86 mg, 0.52 mmol) along with 1-benzhydryl-4-(3-bromopropyl)piperazine (193 mg, 0.52 mmol) were added to the solution. The mixture 35

-39-

was stirred at about 50°C under N₂(g) for about 16 hours. The mixture was partitioned between 1N NaOH (25 mL) and 1:1 EtOAc/Et₂O (30 mL). The organic phase was washed with 1N NaOH (2x10 mL), dried over Na₂SO₄(s), and concentrated in vacuo.

5 The residue was flash chromatographed on silica (15 to 30% acetone/hexanes) to afford 190 mg (80%) of product as the free base. The monohydrochloride salt was prepared by titration of the residue in ethereal solution (15 mL) dropwise with 1M HCl in Et₂O (0.65 mL). After about 30 min. stirring the precipitated salt was filtered and dried in vacuo, 201 mg, 80%. Decomposed at 160°C without melting; LSIMS m/z 454 (MH⁺).

10

Example 10

(Method E_c)

3-(4-[2-[3-(4-Benzhydryl-piperidin-1-yl)-propoxy]phenyl]-thiazol-2-yl)pyridine

4-Benzhydryl-1-(3-chloropropyl)piperidine (329 mg, 1.0 mmol), 2-[2-(pyridin-3-yl)thiazol-4-yl]phenol (318 mg, 1.25 mmol) and n-Bu₄N⁺I⁻(1.0 mmol, 369 mg) in CHCl₃ (3 mL) were stirred vigorously with 0.5N NaOH (10 mL, 5.0 mmol) at about 20°C under N₂(g) for about 72 hours. The mixture was diluted with CHCl₃ (25 mL) and the organic phase was separated, washed with 0.5N NaOH and brine, dried over NaSO₄(s), and concentrated in vacuo. The residue was flash chromatographed on silica (35% acetone/hexanes) to afford 120 mg (22%) of the product as its free base. This material 15 was dissolved in CH₃CN (10 mL) and 1N HCl in Et₂O (0.5 mL, 0.5 mmol) was added dropwise with stirring. After about 30 min. stirring at about 20°C, the mixture was diluted with Et₂O (50 mL) and the dihydrochloride salt was recovered by filtration and 20 dried in vacuo, 130 mg, 21%. mp 159-160°C; LSIMS m/z 547 (MH⁺).

20

Example 11

25

(Method F)

1-Benzhydryl-4-[3-(2-imidazol-1-ylmethyl-phenoxy)-propyl]piperazine

To a stirred partial suspension of Ph₃P (629 mg, 2.4 mmol) and 2-(imidazol-1-yl)methylphenol (350 mg, 2.0 mmol) in dry THF (7.0 mL) under N₂(g) at about 0°C was added diethyl azodicarboxylate (380 mL, 2.4 mmol) dropwise over 2 minutes. During 30 the addition all starting materials dissolved, and 5 minutes after completion of the addition a suspension of 1-benzhydryl-4-(3-hydroxypropyl)piperazine (620 mg, 2.0 mmol) in dry THF (5.0 mL + 2.0 mL rinse) was added dropwise over 5 min. at about 0°C. The resulting solution was stirred for about 20 min. at about 0°C, and 16 hours at about 20°C before concentrating in vacuo to a syrup. The residue was dissolved 35 in Et₂O/EtOAc (25 mL) and 1M HCl in Et₂O (2.0 mL, 2.0 mmol) was added dropwise

-40-

with stirring. Precipitated HCl salts were recovered by filtration and partitioned between 1N NaOH in brine (50 mL) and EtOAc (60 mL). The organic phase was washed with 1N NaOH in brine (2x), saturated Na₂CO₃, and brine, dried over Na₂SO₄(s) and 5 concentrated in vacuo to afford >90% pure product as the free base (650 mg, 70%). The material was dissolved in CHCl₃, titrated with 1M HCl in Et₂O (2.8 mL, 2.8 mmol), and diluted to 20 mL with dry Et₂O to precipitate the dihydrochloride salt, 503 mg. mp 163-165°C (dec); LSIMS m/z 467 (MH⁺).

Example 12

10 (Method G_A)

N-[1-(3-(4-[2-Hydroxy-3-(2-methylbenzothiazol-7-yloxy)-propyl]-piperazin-1-yl)propyl]-1H-benzimidazol-2-yl]-4-methoxy-benzamide

15 4-Methoxy-N-[1-(3-piperazin-1-yl-propyl)-1H-benzimidazol-2-yl]-benzamide (87 mg, 0.22 mmol) and 2-methyl-7-(oxiran-2-ylmethoxy)-benzothiazole (50 mg, 0.22 mmol) were dissolved in 5:1 dioxane/H₂O (1.2 mL) and Amberlite IRA-400® resin ('OH form; 100 mg of 2.3 meq/g, 1.1 eq) was added. The mixture was heated with stirring to about 65°C for about 20 h under N₂(g), and then filtered and concentrated in vacuo. The residue was taken up in 80% CH₃CN/pH 4.5, 2.0 M NH₄OAc (1.5 mL) and injected 20 on a preparative RP-HPLC column ((21.4 mm x 25 cm) Dynamax-60A C18 column) equilibrated in 15% CH₃CN/85% pH 4.5, 50 mM NH₄OAc and eluted (23 mL/min) with a 1% CH₃CN/min gradient. The largest eluting peak was concentrated in vacuo and the residue partitioned between saturated aqueous Na₂CO₃ and EtOAc. The organic 25 phase was dried over Na₂SO₄(s), and concentrated in vacuo to afford 85 mg (63%) of the product as its free base. The free base was dissolved in CHCl₃ (4-5 mL), and 1 M HCl in Et₂O (2.1 eq) was added. The resulting suspension was diluted with dry Et₂O (to ≈ 20 mL) and cooled to about 0-4°C. The precipitated salt was filtered, washed with anhydrous Et₂O and petroleum ether and dried in vacuo to yield 89 mg of the dihydrochloride; LSIMS m/z 615 (MH⁺) ; MP 208°C (dec).

30 Example 13

(Method G_B)

1-(2-Methylbenzothiazol-7-yloxy)-3-[trans-(3-phenyl-bicyclo[2.2.1]hept-2-yl-amino)]propan-2-ol

35 trans-3-Phenyl-bicyclo[2.2.1]hept-2-ylamine hydrochloride (81 mg, 0.362 mmol) and 2-methyl-7-(oxiran-2-ylmethoxy)benzothiazole (81 mg, 0.366 mmol) were dissolved

-41-

in dioxane and 1N NaOH (1.0 eq, 0.362 mmol, 0.362 mL). Amberlite IRA-400® resin (0.16 g, of 2.3 meq/g, 1.05 eq) was added and the gently stirred mixture was heated to about 80°C for about 20 h. under N₂(g). The resin was removed by filtration and the 5 filtrate was concentrated in vacuo. The purified product (88 mg, 59%) was obtained as its free base following preparative RP-HPLC, concentration of peak fractions and extraction as detailed in Method G_A. The free base was dissolved in EtOAc (\approx 3 mL) and 1.1 equivalent of 1N HCl in ether (0.24 mL) was added. After dilution with dry Et₂O and petroleum ether and dried in vacuo; LSIMS m/z 409 (MH⁺); mp 233°C (dec).

10

Example 14

(Method A)

5-[3-(4-Diphenylmethylpiperazin-1-yl)-2-hydroxypropoxy]-1-(2H)-isoquinolone

A solution of N-diphenylmethyl-piperazine (1.02 g, 3.0 mmol) and 5-(2, 3-epoxypropoxy)-1-hydroxy-3, 4-dihydroisoquinoline (295 mg, 1.0 mmol) in 20 mL of EtOH 15 was refluxed for about 2 h. The residue obtained after evaporation of the solvent was chromatographed on silica gel (2% MeOH-CH₂Cl₂) to give 552 mg (87%) of the title compound as an amorphous solid. A HCl solution in ether was added to give quantitatively the di-HCl salt of the title compound; MS 471.2.

20

Example 15

(Method H)

5-[3-(4-Diphenylmethylpiperazin-1-yl)-propoxy]-3,4-dihydro-2-(1H)-naphthalenone

A suspension of sodium hydride (11 mg 60% oil dispersion, 0.28 mmol) and 5-hydroxy-1-tetralone (43 mg, 0.27 mmol) in 5 mL of THF was warmed to about 50°C for about 30 min. After addition of N-diphenylmethyl-N'-(3-bromopropyl)piperazine (100 25 mg, 0.27 mmol) the mixture was stirred at about 50°C for about 3 h. Evaporation of the solvent and silica gel chromatography of the residue (diethyl ether-CH₂Cl₂=1:4) gave 100 mg (83%) of the title compound as an oil; MS 455.4.

Example 16

5-[3-(4-Diphenylmethylpiperazin-1-yl)-2-hydroxypropoxy]-3,4-dihydro-2-(1H)-naphthalenone methyloxime

The product of Example 3 (50 mg, 0.09 mmol) and the methoxyamine-HCl (8 mg, 0.09 mmol) were dissolved in 5 mL of methanol and refluxed for 3 h. The solvent was removed and the residue was chromatographed on silica gel (2.5% MeOH-CH₂Cl₂) to give 37 mg (70%) of the title compound; mp > 183°C decomposition; MS 500.3.

35

-42-

Example 17

5-[3-(4-Diphenylmethylpiperazin-1-yl)-2-hydroxypropoxy]-3,4-dihydro-2-(1H)-naphthalenone oxime

5 The title product was synthesized substantially according to the method of Example 16 but using hydroxylamine-HCl rather than methoxyamine-HCl. 61% yield; m.p. 177°C; M.S. 486.4.

10

15

20

25

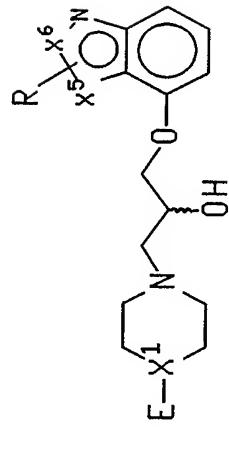
30

35

-43-

Examples 18-32Hydroxy Benzazole Derivatives

5 Compounds of Examples 18-32 having the general formula



were synthesized according to the methods shown.

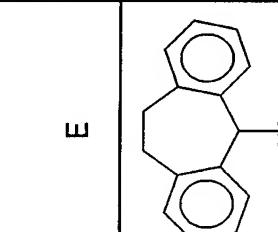
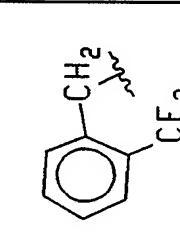
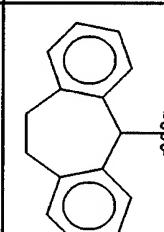
Example Number	E	X ¹	X ⁵	X ⁶	R	Prep. Method	M.P.(°C)	Mass Spec.
18		N	S	C	2-CH ₃	A	154°(dec.)	500
20								

15

20

25

-44-

Example Number	E	X ¹	X ⁵	X ⁶	R	Prep. Method	M.P.(°C)	Mass Spec.
5 19		N	S	C	2-CH ₃	A	150°(dec.)	500
10 20		N	S	C	2-CH ₃	A	205°(dec.)	456
15 21	(Ph) ₂ C-	CH	S	C	2-CH ₃	B	111°(dec.)	473
20 22		N	S	C	2-pyridin-2-yl	A	154°(dec.)	563
25 23	(Ph) ₂ C-	CH	S	C	2-pyridin-2-yl	A	240°(dec.)	536

-45-

Example Number	E	X^1	X^5	X^6	R	Prep. Method	M.P. (°C)	Mass Spec.
24		N	S	C	H	A	181-182°(dec.)	486
25		N	S	C	2-CN	A	140°(dec.)	511
26		N	S	C	2-CH3	A	110-120°(dec.)	458

5

10

15

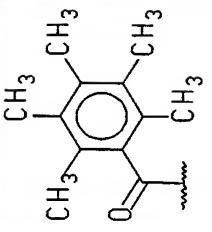
20

25

-46-

Example Number	E	X^1	X^5	X^6	R	Prep. Method	M.P. (°C)	Mass Spec.
27		N	N	S		A	185-190°	487
28		N	N	N	3-CH ₃	A	131°(dec.)	484
29	(Ph) ₂ C-	CH	N	N	3-CH ₃	A	120°(dec.)	457
30	(Ph) ₂ C-	CH	N	CH	3-CH ₃	A	65-75°(dec.)	456
31		N	N	CH	3-CH ₃	A	170°(dec.)	483

-47-

Example Number	E	X ¹	X ⁵	X ⁶	R	Prep. Method	M.P. (°C)	Mass Spec.
32		CH ₃	S	C	2-CH ₃	A	122-135°(dec.)	481

* The R-enantiomer at the 2-propano position ($\geq 86\%$ enantiomeric excess).

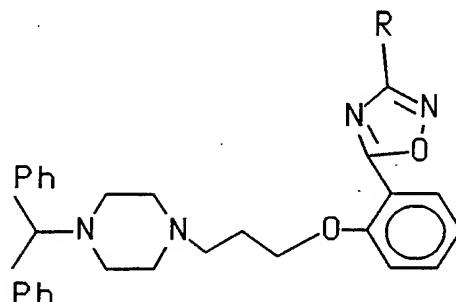
-48-

Examples 33-35

Compounds of Examples 33-35 having the general formula

5

10



were synthesized according to the methods shown.

15

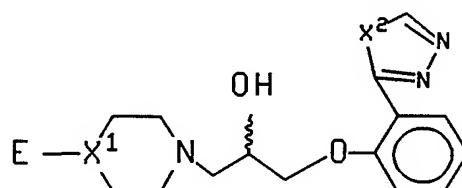
20

Example Numbers	R	Prep. Method	M.P.(°C)	Mass Spec.(MH ⁺)
33	pyridin-3-yl	E _A	228-229°C	532
34	pyridin-2-yl	E _A	158-160°C	532
35	pyridin-4-yl	E _A	223-224°C	532

Examples 36-38

Compounds of Examples 36-38 having the general formula

25



were synthesized according to the methods shown.

30

35

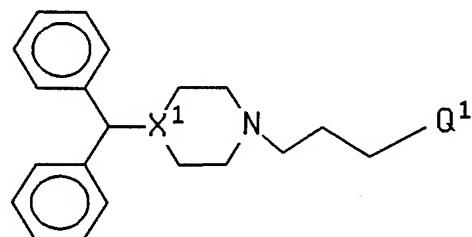
Example Numbers	E	X ¹	X ²	Prep. Method	M.P.(°C)	Mass Spec.
36	(Ph) ₂ CH	N	O	A	210°(dec.)	471
37	PhCH ₂	CH	O	A	128-130°	394
38	(Ph) ₂ CH	N	S	C _B	178-182°	487

-49-

Examples 39-45

Compounds of Examples 39-45 having the general formula

5



10 were synthesized according to the methods shown.

Example Numbers	X¹	Q¹*	Prep. Method	M.P.(°C)	Mass Spec.
15 39	N		E _A	205-210°(dec.)	470
20 40	N		E _B	221.5-223°	470
25 41	N		E _B	233-235.5°	484

-50-

Example Numbers	X ¹	Q ^{1*}	Prep. Method	M.P.(°C)	Mass Spec.	
5	42	N		E _A	180-182°	486
10	43	CH		E _C	67-68°	485
15	44	CH		E _C	135-137°	501
20	45	N		E _A	180°	453
25						

* Bonded through the phenoxy O.

30

35

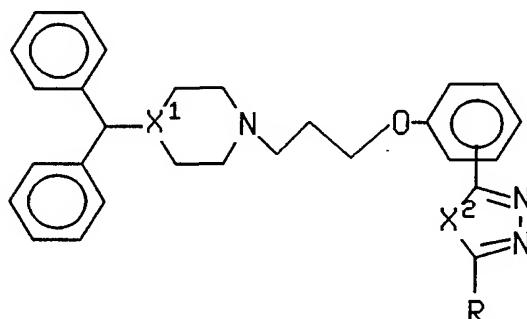
-51-

Examples 46-56

Compounds of Examples 46-56 having the general formula

5

10



were synthesized according to the methods shown.

Ex. No.	X¹	X²	R	Prep. Meth.	M.P.(°C)	Mass Spec.	Position of Diazole
46	CH	O	H	D	104-106°	454	ortho
47	N	O	-CH ₃	E _B	201-202°	469	ortho
48	N	O	-SCH ₃	E _A	226.5-228°	501	ortho
49	N	O	pyridin-3-yl	E _A	*160-161.5°	532	ortho
50	N	S	pyridin-3-yl	E _A	>240°(dec.)	548	ortho
51	N	S	pyridin-4-yl	E _A	>200°(dec.)	548	ortho
52	N	S	H	E _B	163-164.4°	471	meta
53	N	S	H	E _A	250-253.4°	471	ortho
54	N	S	-N(CH ₃) ₂	E _A	*153-154.3°	514	ortho
55	N	S	-CH ₃	E _A	128-130°	485	ortho
56	N	S	phenyl	E _A	152-155°	547	meta

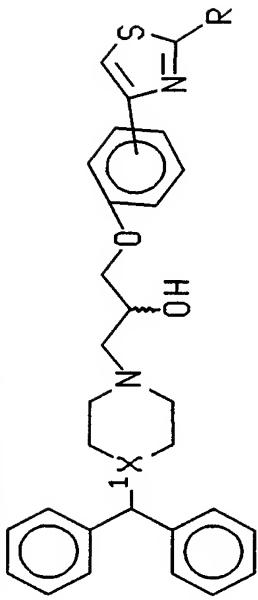
30

*M.P. reported for the free base.

35

-52-

Examples 57-64
 Compounds of Examples 57-64 having the general formula



5

10

were synthesized according to the methods shown.

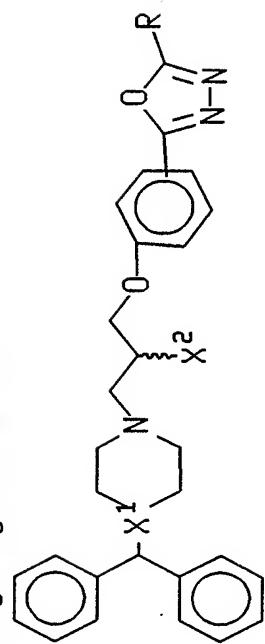
Example Number	X ¹	Position of Thiazole	R	Prep. Method	M.P. (°C)	Mass Spec. (FAB)
57	N	meta	-CH ₃	A	189-191	500
*58	N	meta	phenyl	A	109-110	562
59	N	meta	pyridin-2-yl	A	138-139	563
60	N	meta	pyridin-3-yl	A	163-165	563
61	N	meta	pyridin-4-yl	A	205-206	563
62	N	para	pyridin-2-yl	A	158-159	563
*63	N	para	-CH ₃	A	129-130	500
*64	CH	meta	pyridin-4-yl	B	115-116	563

* The M.P. reported are for the free base.

25

-53-

Compounds of Examples 65-73 having the general formula



5

10

were synthesized according to the methods shown.

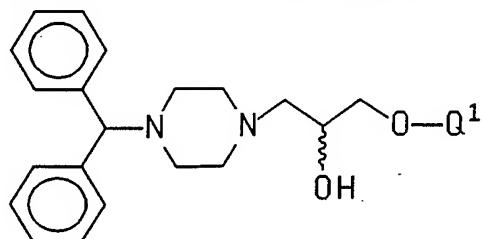
Example Number	X ¹	X ²	Position of Oxadiazole	R	Prep. Method	M.P. (°C)	Mass Spec. (FAB)
65	N	OH	meta	H	A	128-129	471
66	N	OH	meta	-CH ₃	A	185-186	485
67	N	OH	meta	-CH ₂ CH ₃	A	134	499
68	N	OH	para	-CH ₃	A	119	485
69	N	OH	para	-CH ₂ CH ₃	A	204-206	499
70	CH	OH	para	-CH ₂ CH ₃	B	201-202	498
71	CH	OH	meta	-CH ₂ CH ₃	B	150.5	498
72	CH	H	meta	-CH ₂ CH ₃	C	189-193	482
73	CH	H	para	-CH ₃	C	183(dec.)	468

25 *The M.P. reported is for the free base.

-54-

Examples 74-79
 Compounds of Examples 74-79 having the general formula

5



10

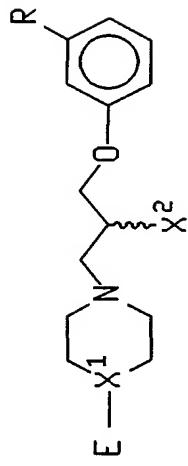
were synthesized according to the methods shown.

Example Number	Q ¹	Prep. Method	M.P.* (°C)	Mass Spec.(FAB)	
15	74		A	116-118	458
20	75		A	123-124	520
25	76		A	176-178	521
30	77		A	139-143	521
	78		A	118-121	444
	79		A	144-145	536

* The M.P. reported is for the free base.

-55-

Examples 80-91
 Compounds of Examples 80-91 having the general formula



were synthesized according to the methods shown.

5

10

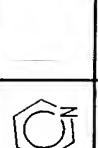
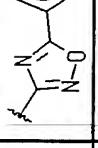
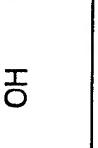
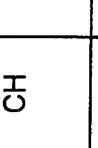
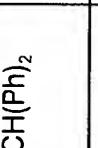
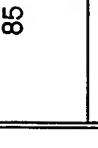
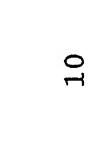
15

20

25

Example Number	E	X ¹	X ²	R	Prep. Method	M.P.(°C)	Mass Spec.(FAB)
80	-CH(Ph) ₂	N	OH		A	194.5-195	484
81	-CH(Ph) ₂	N	OH		A	190-193	548
82	-CH(Ph) ₂	N	OH		A	224	548
83	-CH(Ph) ₂	N	OH		A	120	548

-56-

Example Number	E	X'	X ²	R	Prep. Method	M.P.(°C)	Spec.(FAB)	Mass
84	-CH(Ph) ₂	CH	OH		B	193-194	484	
85	-CH(Ph) ₂	CH	OH		B	134	547	
86	-CH(Ph) ₂	CH	OH		B	126-131	547.3	
87	-CH(Ph) ₂	CH	OH		B	223.5	547	
88	-CH(Ph) ₂	CH	H		C	163	531	
89	-CH(Ph) ₂	CH	H		C	94-96	531	
*90	-CH(Ph) ₂	CH	H		C	116-147	531	
91		N	OH		C	133-146	574	

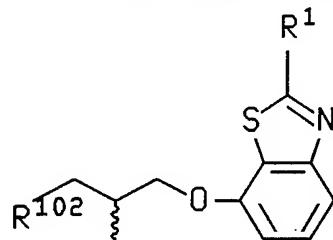
* The M.P. reported is for the free base.

-57-

EXAMPLES 92-135

Compounds of Examples 92-135 having the general formula

5



10

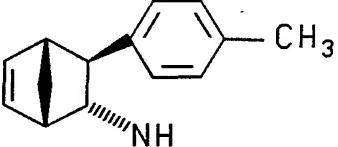
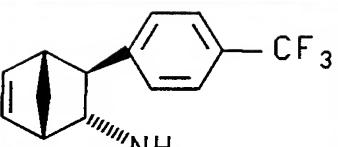
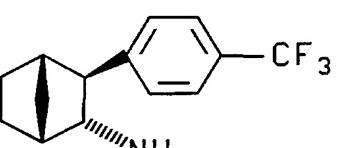
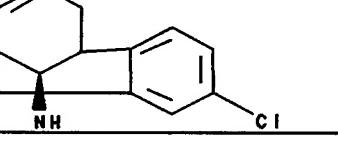
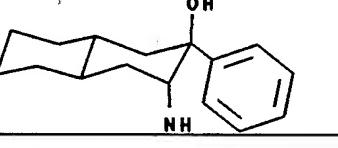
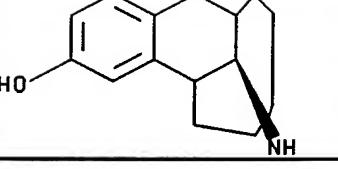
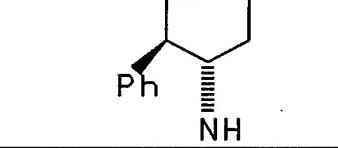
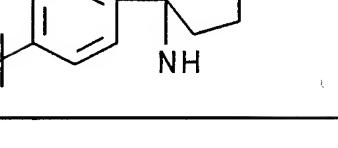
were synthesized according to the methods shown.

Ex. No.	R ¹⁰² Bonded through the amino	R ¹	Prep. Meth.	M.P. (°C)	Mass Spec.
92		Me	G _B	180(dec.)	383
93		Me	G _B	145-150	413
94		Me	G _B	165(dec.)	517
95		Me	G _B	188-197(dec.)	449

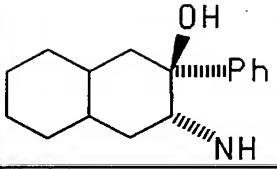
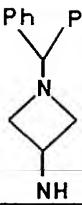
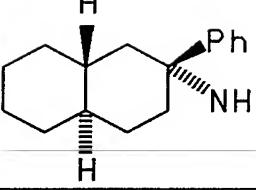
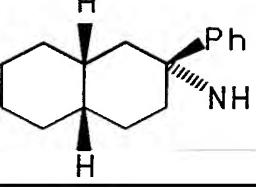
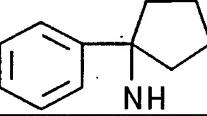
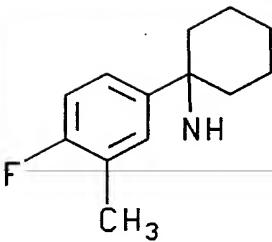
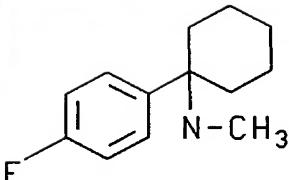
-58-

Ex. No.	R^{102} Bonded through the amino	R^1	Prep. Meth.	M.P. (°C)	Mass Spec.
5	96 	Me	G _B	160-167(dec.)	449
10	97 	Me	A	186(dec.)	433
15	98 	Me	G _B	149-168(dec.)	484
20	99 	Me	G _B	185-195	395
25	100 	Me	G _B	233(dec.)	409
30	101 	Me	G _B	200(dec.)	407

-59-

Ex. No.	R^{102} Bonded through the amino	R^1	Prep. Meth.	M.P. (°C)	Mass Spec.
5	102 	Me	A	150-160(dec.)	421
10	103 	Me	A	152-159	475
15	104 	Me	A	110-125	477
20	105 	Me	G _B	230-236	441
25	106 	Me	G _A	160-165	467
30	107 	Me	G _A	200(dec.)	453
35	108 	Me	G _B	123(dec.)	383
40	109 	Me	G _B	195-197	439

-60-

Ex. No.	R^{102} Bonded through the amino	R^1	Prep. Meth.	M.P. (°C)	Mass Spec.
5	110 	Me	G _B	187-189	467
10	111 	Me		55	460
15	112 	Me	G _A	156(dec).	451
20	113 	Me	G _A	154(dec).	451
25	114 	Me	G _B	151-156	383
30	115 	Me	G _B	161(dec).	429
35	116 	Me	A	186	429

-61-

Ex. No.	R^{102} Bonded through the amino	R^1	Prep. Meth.	M.P. (°C)	Mass Spec.
5 117		Me	G_B	155-160	542
10 118		Me	A	127-133	431
15 119		Me	G_B	122-125	542
20 120		Me	G_B	208-209	431
25 121		Me	A	108(dec).	476
30 122		Me	A	110(dec).	476
35 123		Me	A	207-211(dec).	508

-62-

Ex. No.	R^{102} Bonded through the amino	R^1	Prep. Meth.	M.P. (°C)	Mass Spec.
5 124		Me	A	208-212(dec).	508
10 125		Me	G_A		377
15 126		Me	G_A		377
20 127		Me	A	135(dec).	441
25 128		Me	G_B	120-127(dec).	463
30 129		n-Bu	G_B	186	425
35 130		n-Bu	G_B	177-181	474

-63-

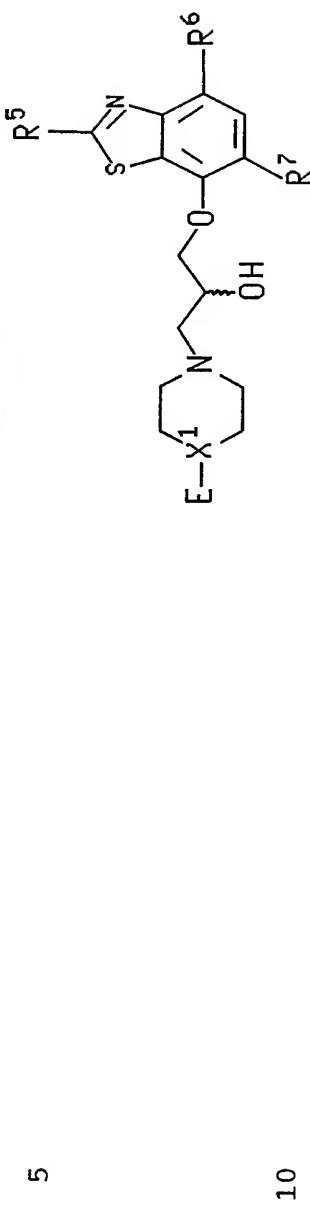
Ex. No.	R^{102} Bonded through the amino	R^1	Prep. Meth.	M.P. (°C)	Mass Spec.
5	*131	i-Pr	G _B	197(dec).	460
10	*132	i-Pr	G _B	222	405
15	*133	n-Bu	G _B	209(dec).	439
20	*134	i-Pr	G _B	145	470
25	*135	i-Pr	G _B		

* R-isomer at the propan-2-ol.

-64-

EXAMPLES 136-158
 Compounds of Examples 136-158 having the general formula

5



were synthesized according to the methods shown.

15

Example Number	E	X'	R ⁵	R ⁶	R ⁷	Prep. Meth.	M.P. (°C)	Mass Spec.
136	N	-CH ₃	H	H	H	G _A	195-208° (dec) (dHCl)	615
20								

25

-65-

	Example Number	E	X ¹	R ⁵	R ⁶	R ⁷	Prep. Meth.	M.P. (°C)	Mass Spec.
5	137		C	-CH ₃	H	H	G _b	230-235° (dec)	485
10	138		N	-NMe ₂	H	H	A	160°	529
15	139		N	pyridin-3-yl	H	H	A	145-150° (dec)	563
20	140		N	i-Pr	H	H	A	135°(dec)	528

-66-

Example Number	E	X ¹	R ⁵	R ⁶	R ⁷	Prep. Meth.	M.P. (°C)	Mass Spec.
5	141	N	methyl	NO ₂	H	%	oil	545
10	*142	N	piperazin-1-yl	H	H	A**	145°	570
15	*143	N	pyridin-4-yl	H	H	A	156°(dec)	563
20	*144	N	ethyl	H	H	A	160°(dec)	514

-67-

Example Number	E	X ¹	R ⁵	R ⁶	R ⁷	Prep. Meth.	M.P. (°C)	Mass Spec.
5 145		N	n-butyl	H	H	A	136°(dec)	542
10 146		N	4-methyl piperazin-2-yl	H	H	A	>165°(dec)	584
15 147		N	methyl	amino	H	%	66-68°	515
20 148		N	methyl	-NHCO-CH ₃	H	%	glass	557

-68-

Example Number	E	X'	R ⁵	R ⁶	R ⁷	Prep. Meth.	M.P. (°C)	Mass Spec.
5 149		N	methyl	H	-CH ₂ CH=CH ₂	A	hygroscopic solid	498
10 150		N	morpholino	H	H	A	186°(dec)	529
15 151		N	-CH ₂ CHOH-(CH ₃) ₂	H	H	G _A	156-160°(dec)	594
20 152		N	methyl	H	H	G _A	152-156°(dec)	536

-69-

Example Number	E	X ¹	R ⁵	R ⁶	R ⁷	Prep. Meth.	M.P. (°C)	Mass Spec.
5 *153		N	-CONH ₂	H	H	G _A	160°(dec)	525
10 *154		N	methyl	H	H	A	208-210°(dec)	500
15 155		N	morpholino	H	H	A	142-146°(dec)	571
20 *156		N	-CH ₂ CH(OH)-(CH ₃) ₂	H	H	A	149-153°(dec)	558

-70-

Example Number	E	X ¹	R ⁵	R ⁶	R ⁷	Prep. Meth.	M.P. (°C)	Mass Spec.
5	157	N	methyl	-NHBn	H	%	138-141°	605
10	158	-CH(Ph) ₂	N	methyl	Cl	H	A	70-76°(free base) 234-235°(HCl salt)

* R-isomer at propan-2-ol position.

† S-isomer at propan-2-ol position.

** Prepared from 2-(4-trifluoroacetyl-piperazin-1-yl)benzothiazol-7-ol (Preparation 86) with subsequent deacetylation at pH 12 during extractive work-up.

% The preparation of this compound is described herein below.

Preparation of Examples 141, 147 and 157

The nitration of 7-methoxy-2-methylbenzothiazole was carried out as described for the nitration of benzothiazole (Ward, E.R.; Poesche, W.H.; J. Chem. Soc. 1961, 5 2825). The nitration produces a mixture of 4-and 6-nitrobenzothiazoles which were separated by column chromatography (silica gel, CH_2Cl_2) to give the 7-methoxy-2-methyl-4-nitrobenzothiazole as a white solid (31%).

7-Hydroxy-2-methyl-4-nitrobenzothiazole was prepared from 7-methoxy-2-methyl-4-nitrobenzothiazole by treatment with solid pyridine hydrochloride as described 10 in Preparation 1 (91%).

To 7-hydroxy-2-methyl-4-nitrobenzothiazole (0.88 g, 4.2 mmol) in DMF (5 mL) was added NaH (0.184 g of 60% oil dispersion, 4.6 mmol) portionwise. The reaction was stirred at room temperature for about 30 minutes at which time epibromohydrin (394 μL , 4.6 mmol) was added in one portion and the reaction then heated at about 15 60°C. To push the reaction towards completion, additional epibromohydrin (400 μL) was added. The reaction was poured into water and extracted with ethyl acetate. The organic extracts were combined, washed with H_2O , dried over Na_2SO_4 and the solvent removed by rotary evaporation. The resulting dark oil (960 mg, 86%) was used without further purification.

20 The epoxide (0.39 g, 1.5 mmol) and 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine (0.847 g, 3.0 mmol) were dissolved in 1:1 EtOH/dioxane (10 mL) and heated at reflux for about 4 h. The solvent was removed by rotary evaporation and the crude product purified by column chromatography (silica gel, 5% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give the piperazinyl alcohol (0.651g, 79%), [EXAMPLE 141].

25 This material (650 mg, 1.2 mmols) was dissolved in 1:1 dioxane/ CH_3OH (6 mL) to which was added $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (571 mg, 2.4 mmol) and finally sodium borohydride (454 mg, 12.0 mmol) was added portionwise. The reaction was stirred at room temperature for 2 h. The reaction was filtered and the filtrate concentrated by rotary evaporation. The residue was dissolved in CH_2Cl_2 and washed with H_2O and brine and 30 the organic layer dried over Na_2SO_4 . The solvent was removed by rotary evaporation and the crude residue purified by column chromatography (silica gel, 9:1:2 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{hexane}$) to give the 4-aminobenzothiazole derivative [EXAMPLE 147] (125 mg, 20%).

35 The 4-aminobenzothiazole derivative (57 mg, 0.11 mmol) was added to a suspension of $\text{NaBH}(\text{OAc})_3$ (93 mg, 0.44 mmol) in dichloroethane (1 mL) followed by

-72-

addition of benzaldehyde (110 μ L, 0.11 mmol) and Na_2SO_4 . The reaction was stirred at room temperature for about 48 h. The reaction was diluted with CH_2Cl_2 , washed with saturated aqueous Na_2CO_3 and brine and dried over Na_2SO_4 . The solvent was 5 removed by rotary evaporation and the crude product purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2 \rightarrow 10\% \text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give the product of [Example 157], 1-(4-Benzylamino-2-methyl-benzothiazol-7-yloxy)-3-[4-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-piperazin-1-yl]-propan-2-ol, as the free base (40 mg, 61%). The hydrochloride salt was formed by dissolving the free base in $\text{Et}_2\text{O}/\text{CHCl}_3$ 10 and treating with 1N HCl/Et₂O. mp=138-141°C; MS=605.

Preparation of Example 148

N-(7-{3-[4-(10,11,Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-2-hydroxy-propoxy}-2-methyl-benzothiazol-4-yl)-acetamide

To the 4-aminobenzothiazole derivative (compound of Example 147) (0.035 g, 15 0.07 mmol) dissolved in CH_2Cl_2 (1 mL) was added triethylamine (20 μ L, 0.14 mmol), acetic anhydride (20 μ L) and catalytic amount of DMAP. The reaction was stirred at room temperature for several hours at which time water was added and the layers separated. The organic layer was dried over Na_2SO_4 and evaporated to a yellow oil which was purified by column chromatography. 20 This bis-acetylated material was treated with KOH/CH₃OH for 24 h. to give the title compound. MS=558.

25

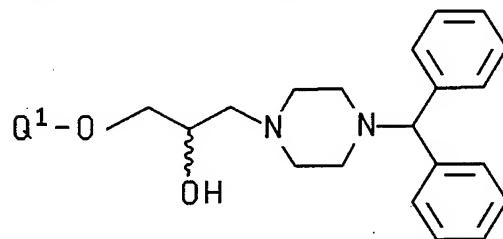
30

35

-73-

EXAMPLES 159-163

Compounds of Examples 159-163 having the general formula



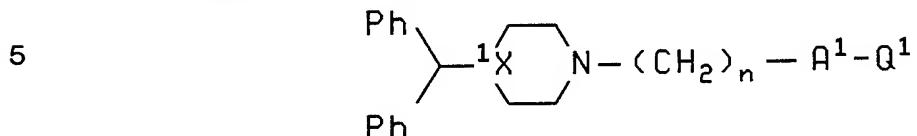
were synthesized according to the methods shown.

Example Number	Q ¹	Prep. Method	Mass Spec.
159		A	471
160		A	470
161		A	485
162		A	485
163		A	575

-74-

EXAMPLES 164-170

Compounds of Examples 164-170 having the general formula



were synthesized according to the methods shown.

Example Number	X ¹	n	-A ¹ -Q ¹ **	Prep. Method	M.P. (°C)	Mass Spec.
+164	N	2		D	67-71.8°	506
165	CH	3		*	95-103°	440
166	CH	3		*	>300°(dec)	427
+167	CH	3		*	65-76°	426
168	CH	3		*	>300°(dec)	441
169	CH	3		*	>300°(dec)	441
170	N	3		E _A	136-137°	444

* These compounds were synthesized according to the procedures on the following pages.

+ The M.P. reported is for the free base.

35 ** A¹ is the phenoxy O and it is directly bonded to the methylene group of the general structure shown at the top of the page.

Preparation of Examples 164-170

4-Benzhydrylpiperidine hydrochloride (4.20g, 15.0 mmol) stirred in dioxane (25 mL)/6N. aq.NaOH (2.5 mL) with diisopropylethylamine (2.65 mL) was treated with 3-bromopropyl-(2, 3-dinitrophenyl) ether (5.05 g, 16.6 mmol) at about 20°C for about 16h followed by about 80°C for about 3 h. The reaction mixture was concentrated in vacuo and partitioned between EtOAc and 1N NaOH. The organic phase was dried over MgSO₄(s), concentrated in vacuo to ≈25 mL and diluted to cloudiness with diisopropyl ether. The product was precipitated as the HCl salt by addition of 1 M HCl in Et₂O (18 mL, 18 mmol). The precipitated crystals of 1-[3-[4-(benzhydryl)piperidin-1-yl]propoxy]-2,3-dinitrophenol were filtered, washed with diisopropyl ether and petroleum ether and dried (6.85g; LSIMS m/z 476).

The dinitrophenyl amine HCl salt, synthesized in the previous step, (2.02 g, 3.95 mmol) in MeOH (200 ml) was hydrogenated (15-60 psi, 2-20h) in the presence of 5-10% Pd on carbon catalyst (200 mg). Following removal of catalyst by centrifugation or filtration under a N₂(g) atmosphere and removal of solvent in vacuo (30-35°C) the air-sensitive diaminophenyl intermediate was obtained (>90% purity; 100% recovery; LSIMS m/z 416) and used directly in subsequent reactions.

Benzimidazoles (Examples 165 and 167): The appropriate diaminophenyl intermediate synthesized above was dissolved in excess formic acid (Example 167) or acetic acid (Example 165) (≈2-5 g/100 mL) and the stirred solution was heated to reflux under dry N₂(g) for about 8-16h. Excess acid was removed in vacuo (30-40°C) and the residue was partitioned between EtOAc and aqueous 5% Na₂CO₃ or 1N NaOH. The organic phase was washed with brine, dried over Na₂SO₄, concentrated in vacuo and chromatographed on silica (10-15% MeOH in EtOAc) to afford the benzimidazole products (55-85% yields) as the free bases.

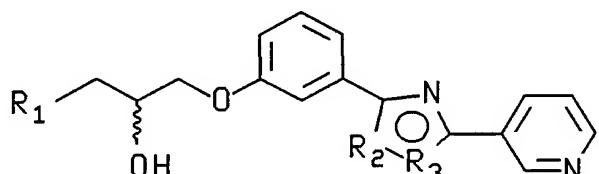
Benzotriazoles (Example 166): The appropriate diaminophenyl intermediate (1.0 g, 2.57 mmol) was dissolved in 50% aqueous AcOH (50 mL). While stirring vigorously 0.84 M aqueous NaNO₂ (3.1 mL, 2.6 mmol) was added dropwise over 10 min. at 0-5°C. After 15 minutes it was concentrated in vacuo and partitioned between EtOAc and H₂O (with the pH of the aqueous phase adjusted to 9-10). The organic phase was washed with brine, dried over Na₂SO₄, concentrated in vacuo and chromatographed on silica (15% MeOH/EtOAc) to afford the benzotriazole (Example 166) as the free base (60-77% yield; 0.63-0.81 g).

-76-

N-Methyl Benzotriazoles (Examples 168 and 169): Benzotriazole free base (from above; 155 mg, 0.36 mmol) in CH_2Cl_2 (2.5 mL) was treated while stirring with etheral diazomethane (2-10 eq.). After about 2h (10-20°C) the solvent and excess diazomethane were removed in vacuo and the residue was chromatographed on silica (Chromatotron; 1% conc. NH_4OH ; 1.5% MeOH, 97.5% (CHCl_3)) to afford (36%; 57 mg) 2-N-methyl benzotriazole derivative (Example 169) and (15%; 24 mg) 3-N-methyl benzotriazole (Example 168).

EXAMPLES 171-180

10 Compounds of Examples 171-180 having the general formula



15

were synthesized according to the methods shown. *The M.P. reported is for the free base.

Example Number	$\text{R}_1(=\text{NR}^{101}\text{R}^{102})$	R_2	R_3	Prep. Method	M.P. (°C)	Mass Spec.
171		N	O	A	192-193°	547
172		N	O	A	125°	467

-77-

Example Number	$R_1(=NR^{101}R^{102})$	R_2	R_3	Prep. Method	M.P. (°C)	Mass Spec.	
5	173		N	O	A	119°	467
10	174		O	N	A	115-116°	467
15	*175		O	N	A	foam	467
20	*176		O	N	A	foam	487
25							
30							

-78-

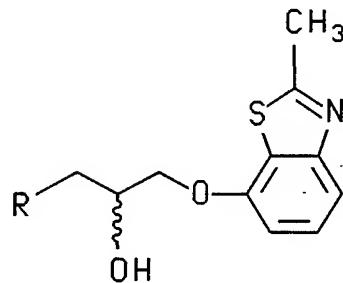
Example Number	$R_1 (=NR^{101}R^{102})$	R_2	R_3	Prep. Method	M.P. (°C)	Mass Spec.
5	*177 	N	O	A	foam	467
10	*178 	O	N	A	foam	467
15	*179 	N	O	A	86-89°	563
20	*180 	O	N	A	82-83°	563
25						
30						
35						

-79-

Examples 181-193

Compounds of Examples 181-193 having the general formula

5

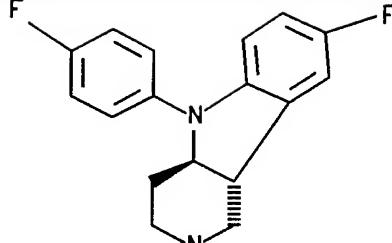


10

were synthesized according to Method G_A using the free base or salt form of the amines and 3.0 equivalents of Amberlite IRA-400 resin.

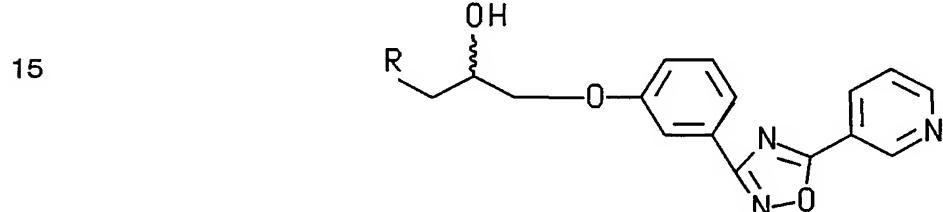
Example Number	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino group	HPLC Ret. Time (min.)	LC-MS (MH ⁺)
181	Cyclohexylamino	2.83	321
182	1-Amino-4-methylcyclohexane	3.05, 3.12	335
183	1-Amino-3-methylcyclohexane	3.06	335
184	1-Amino-4-t-butylcyclohexane	3.81	377
185	1-Amino-1-phenylcyclohexane	3.45	397
186	Diphenylmethylamino	3.60	405
187	1-amino-1,2,3,4-tetrahydronaphthalene	3.15	385
188		3.02	355
189	3-(aminomethyl)benzo[b]thiophene	3.69	385
190	1-amino-1,2-diphenylethane	3.59	419
191	2-amino-4-phenylbutane	4.21, 4.31	371
192	4-(2-phenylethyl)piperazin-1-yl	3.05	412

-80-

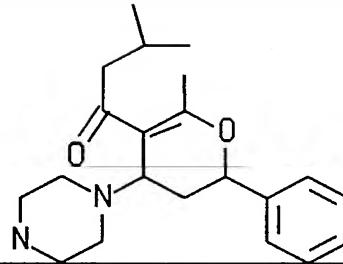
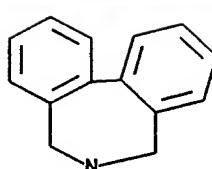
Example Number	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino group	HPLC Ret. Time (min.)	LC-MS (MH ⁺)
5 193		4.48	508
10			

Examples 194-222

Compounds of Examples 194-222 having the general formula

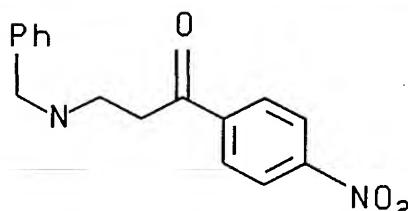
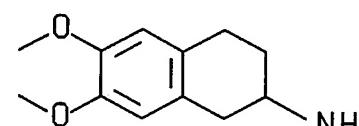
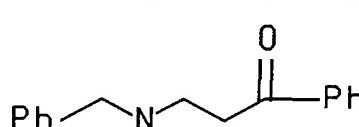
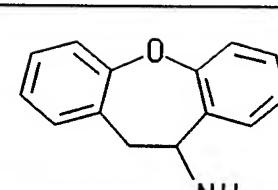
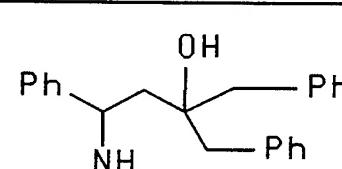
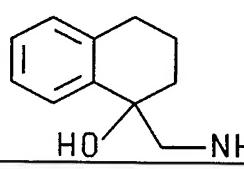
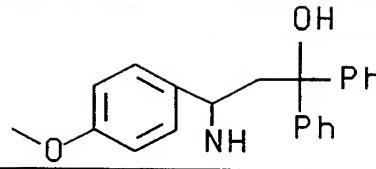


20 were synthesized according to the methods shown.

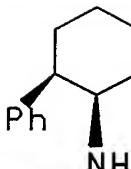
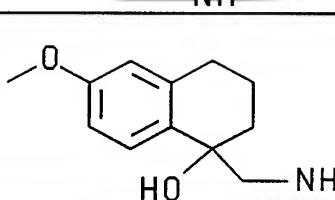
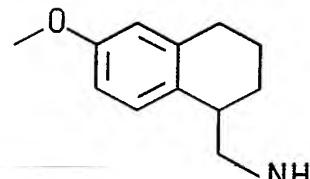
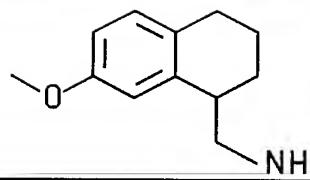
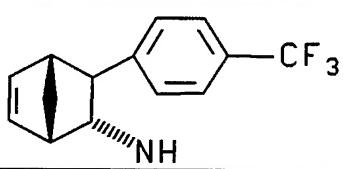
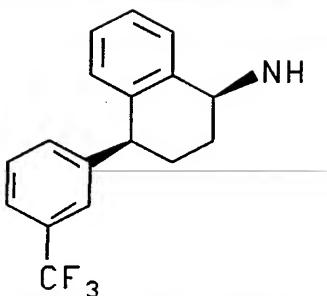
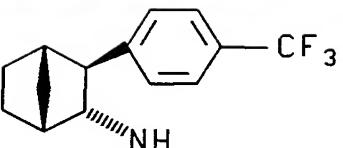
Example Number	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino group	HPLC Ret. Time (min.)	Mass Spec. (MH ⁺)
194	4-(3-hydroxy-3,3-diphenylpropyl)piperazin-1-yl	3.99	592
195	4-[2-(trifluoromethyl)benzyl]piperazin-1-yl	4.11	540
196		4.05	638
197		3.88	491

Example Number	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino group	HPLC Ret. Time (min.)	Mass Spec. (MH ⁺)
5 198		3.91	689
10 199		3.83	569
15 200		3.53	547
20 201	N,N-Bis-[2-(3,4-dimethoxyphenyl)ethyl]amino	3.97	641
202	4-(3-Trifluoromethylphenyl)piperazin-1-yl	3.88	526
203		3.20	489
25 204		3.54	559
30 205		4.23	555

-82-

Example Number	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino group	HPLC Ret. Time (min.)	Mass Spec. (MH ⁺)
5	206 1-Amino-1-benzylcyclopentane	3.85	471
10	207 	3.53	580
15	208 	3.41	503
20	209 	3.25	535
25	210 	3.20	528
30	211 	4.08	507
35	212 	5.04	627
40	213 	3.54	473
45	214 	4.83	629

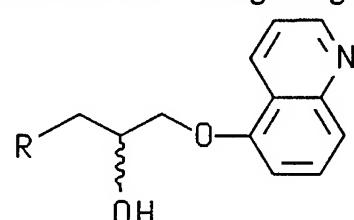
-83-

Example Number	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino group	HPLC Ret. Time (min.)	Mass Spec. (MH ⁺)	
5	215		3.95	471
10	216		3.53	503
15	217		3.87	487
20	218		3.86	487
25	219		4.32	549
30	220		4.74	587
35	221		4.45	551

Example Number	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino group	HPLC Ret. Time (min.)	Mass Spec. (MH ⁺)
5 222		3.99	483

Examples 223-234

Compounds of Examples 223-234 having the general formula

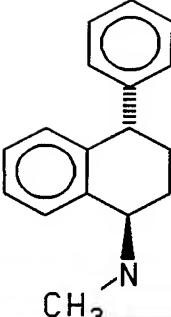
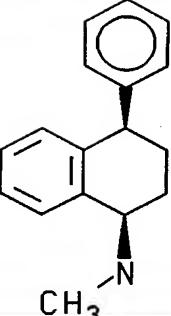
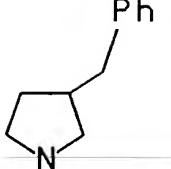
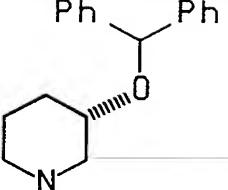
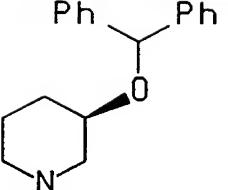


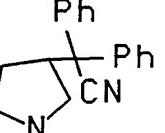
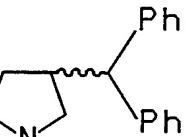
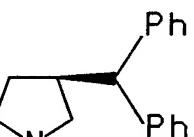
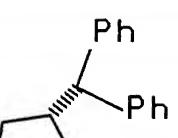
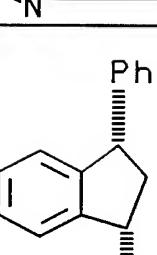
15

were synthesized according to Method A.

Example	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino	RP-HPLC Retention Time (min.)	LC-MS (MH ⁺)	MP (°C)
20 223		N.T.	507	>175°C
25 224		4.60 min.	439	162°C

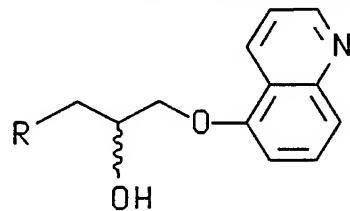
-85-

Example	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino	RP-HPLC Retention Time (min.)	LC-MS (MH ⁺)	MP (°C)
5 225		4.81 min.	439	175°C
10 226		N.T.	439	159°C
15 227		N.T.	363	96.0
20 228		4.64	469	115
25 229		4.64	469	N.T.

Example	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino	RP-HPLC Retention Time (min.)	LC-MS (MH ⁺)	MP (°C)
5 230		N.T.	464	111
10 231		N.T.	439	125
15 232		N.T.	439	119
20 233		N.T.	439	116
25 234		N.T.	425	141

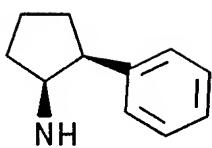
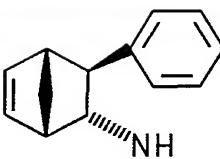
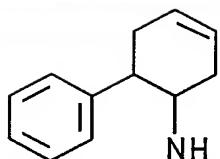
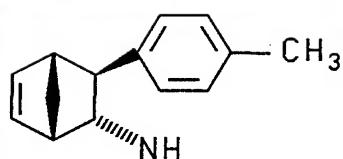
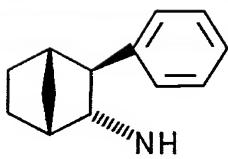
N.T. = Not taken.

Examples 235-258

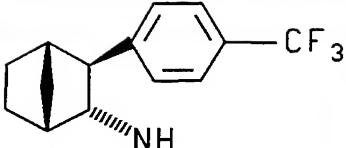
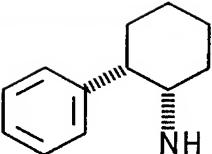
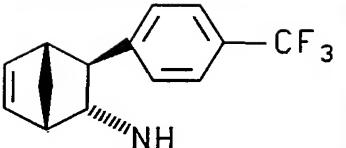
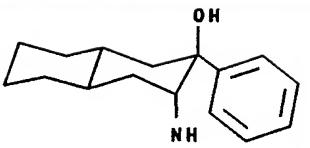


35 were synthesized according to Method B.

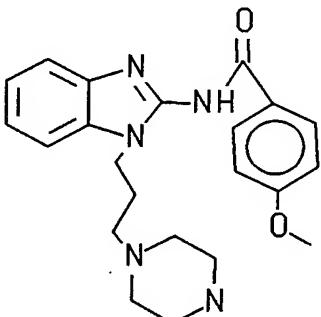
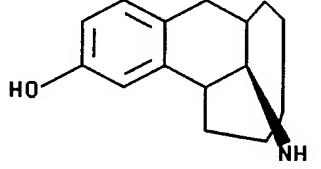
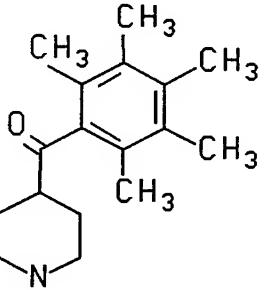
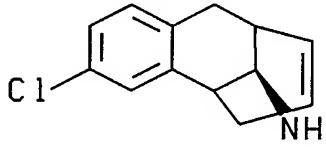
-87-

Example	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino	RP-HPLC Retention Time (min.)	LC-MS (MH ⁺)
5 235		2.93	363
10 236		3.21	387
15 237		3.10	375
20 238		3.37	401
25 239		3.25	389

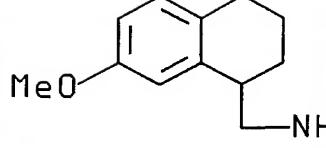
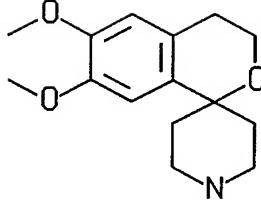
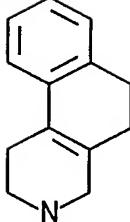
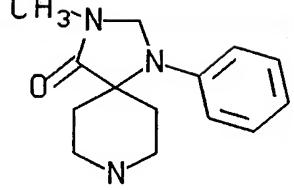
-88-

Example	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino	RP-HPLC Retention Time (min.)	LC-MS (MH ⁺)
5 240		3.73	457
10 241		3.16	377
15 242		3.16	377
20 243		3.62	455
25 244		3.26	447
30			

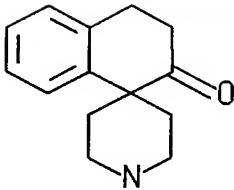
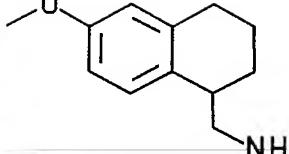
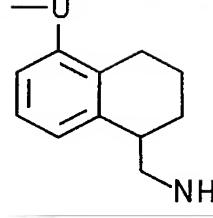
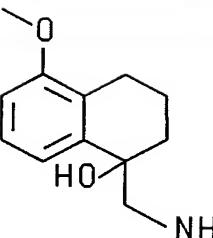
-89-

Example	R ($=\text{NR}^{101}\text{R}^{102}$) Bonded through the amino	RP-HPLC Retention Time (min.)	LC-MS (MH^+)
5 10 15 20 25 30 35	245  246  247  248 	3.32 3.29 3.63 3.44	595 433 461 421

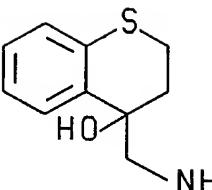
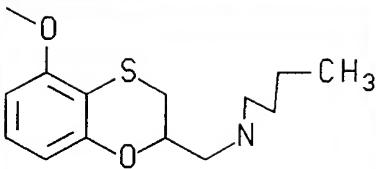
-90-

Example	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino	RP-HPLC Retention Time (min.)	LC-MS (MH ⁺)
5 249		3.19	393
10 250		2.89	465
15 251		3.10, 3.27 (~1:1 diastereomers)	387
20 252		2.93	447

-91-

Example	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino	RP-HPLC Retention Time (min.)	LC-MS (MH ⁺)
5 253		3.05	417
10 254		3.09	393
15 255		3.21	393
20 256		2.86	409

-92-

Example	R (=NR ¹⁰¹ R ¹⁰²) Bonded through the amino	RP-HPLC Retention Time (min.)	LC-MS (MH ⁺)
5 257		2.81	397
10 258		3.91	469

20

25

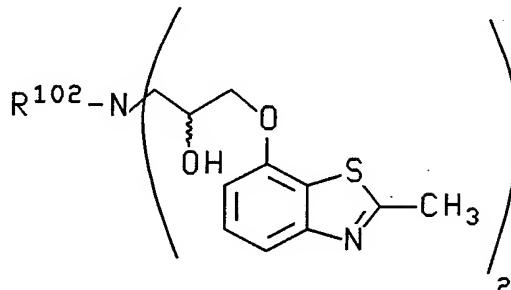
30

35

-93-

Examples 259-261

Compounds of Examples 259-261 having the general formula



were synthesized according to the methods shown.

Example Number	R¹⁰²	Prep. Method	MP (°C)	Anal. RP-HPLC Retention Time	LC-MS (MH⁺)
259		G _A	75°C	5.09 min.	604
260		G _A	93°C	4.97 min.	634
261		G _A	N.T.	2 diastereomers 4.75 min. 4.90 min.	628 628

* The M.P. reported is for the free base.

N.T. = Not taken.

-94-

EXAMPLE 262

5-[2-(4-Benzhydryl-piperidin-1-yloxy)ethoxy]quinoline

To 0.13 g (3.25 mmol) of NaH (60% oil dispersion) in 2 ml of DMF at room temperature, was added portionwise 0.785 g (2.94 mmol) of N-hydroxybenzhydryl-piperidine. After bubbling had stopped, stirring was continued for an additional 15 minutes, 0.741 g (2.94 mmol) of 5-(2-bromoethoxy)quinoline was added. The mixture was stirred for about 10 minutes and heated to reflux for about 6 hours. The resulting black solution was cooled to room temperature, poured over ice and extracted with 1:1 Et₂O/EtOAc. These were dried over MgSO₄(s) filtered and concentrated in vacuo to give a black oil, 1.18 g. This material was chromatographed on silica gel using a gradient of 2 to 4% MeOH/CHCl₃ as eluent, to yield 60 mg of a yellow oily solid. This material was dissolved in minimal CHCl₃, diluted 4X with dry Et₂O and precipitated as the monohydrochloride salt by dropwise addition of 1 equivalent of 1 molar HCl in Et₂O. The resulting white solid was filtered and dried in vacuo to yield 65 mg of the desired product, LSIMS, MH⁺ at 439, analytical RP-HPLC, 6.95 min.

Example 263

1-(4-Benzhydryl-piperazin-1-yl)-3-(2-pyridin-3-yl-8-oxa-1-thia-3-aza-cyclo-penta[a]inden-7-yloxy)-propan-2-ol

3-Oxo-7-methoxybenzofuran (500 mg, 3.29 mmol) was dissolved in CCl₄ (15 mL) and treated with a solution of Br₂ (0.17 mL, 3.29 mmol) in CCl₄ (5 mL). After about 10 min. the solvent was removed in vacuo. The resulting oil was dissolved in acetone (20 mL), treated with thioisonicotinamide (454 mg, 3.29 mmol) and refluxed for about 18 h. The dark mixture was cooled and CH₂Cl₂ was added to precipitate product which was filtered and chromatographed on silica (R_f 0.25, 8% MeOH/CH₂Cl₂) to provide 30 mg of chromatographically pure material. This anisole product was converted to the phenol by the method described in Preparation 16 below. The glycidyl ether of this material was prepared according to the method described in Preparation 69 below. Finally the title compound was prepared according to Method A as described in Example 2 above. The final product was purified by column chromatography on silica gel eluting with 5% MeOH/CH₂Cl₂ to provide 12.3 mg of a solid which was triturated with Et₂O/hexanes to provide a yellow powder. (R_f 0.41, 10% MeOH/CH₂Cl₂). FAB MS, 563.2.

-95-

Example 264

cis-7-{4-[4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-but-2-enyloxy}-2-methyl-benzothiazole

5 The title compound was prepared according to Method G_A from cis-7-(3-chloro-allyloxy)-2-methyl-benzothiazole and 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine. mp 114°C; LSIMS m/z 496. The cis-7-(3-chloro-allyloxy)-2-methyl-benzothiazole was prepared by Method IV, with cis-1,4-dichloro-2-butene as the alkylating agent.

10

Example 265

trans-7-{4-[4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-but-2-enyloxy}-2-methyl-benzothiazole

15 The title compound was prepared according to Method G_A from trans-7-(3-chloro-allyloxy)-2-methyl-benzothiazole and 1-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)piperazine. mp 151-152°C; LSIMS m/z 496. The trans-7-(3-chloro-allyloxy)-2-methyl-benzothiazole was prepared by Method IV with trans-1,4-dichloro-2-butene as the alkylating agent.

20

Example 266

1-[4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-2-methyl-4-(2-methylbenzothiazol-7-yloxy-butan-2-ol

25

The title compound was prepared according to Method A from 2-methyl-7-[2-(2-methyl-oxiranyl)-ethoxy]benzothiazole and 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine. mp 137-138°C; LSIMS m/z 528. The 2-methyl-7-[2-(2-methyl-oxiranyl)-ethoxy]benzothiazole was prepared by the method described in Preparation 95.

Example 267

2-Methyl-4-(2-methyl-benzothiazol-7-yloxy)-1-[4-(2-propylsulfanyl-phenyl)-piperazin-1-yl]-butan-2-ol hydrochloride

30

The title compound was prepared according to Method A from 2-methyl-7-[2-(2-methyl-oxiranyl)-ethoxy]benzothiazole and 1-(2-thiopropylphenyl)piperazine. mp 129-130°C; LSIMS m/z 486. The 2-methyl-7-[2-(2-methyl-oxiranyl)-ethoxy]benzothiazole was prepared by the method described in Preparation 95.

Example 2682-[4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-6-(2-methyl-benzothiazol-7-yloxy)-cyclohexanol

5 The title compound was prepared according to Method A from 2-methyl-7-(7-oxa-bicyclo[4.1.0]hept-2-yloxy)-benzothiazole and 1-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)piperazine with dioxane/toluene (2:1) as the solvent. mp 207°C (decomposition); LSIMS m/z 540. The 2-methyl-7-(7-oxa-bicyclo[4.1.0]hept-2-yloxy)-benzothiazole was prepared according to Method IV using THF as the solvent and 4-10 bromo-2-oxa-bicyclo[4.1.0]heptane as the alkylating agent.

Example 2691-(1-Benzhydryl-azetidin-3-ylamino)-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol

15 The title compound was prepared according to Method A from 2-methyl-7-(oxiranyl-2-ylmethoxy)benzothiazole and 3-amino-1-benzhydrylazetidine with dioxane/ethanol (1:1) as the solvent. mp 55°C; LSIMS m/z 460. The 3-amino-1-benzhydrylazetidine was prepared as described in Preparation 96.

20 The following section describes the preparation of starting materials for use in synthesizing the compounds of this invention. Other starting materials not described in the following section are available commercially or through literature methods well-known to those skilled in the art.

Preparation 12-Methyl-benzothiazol-7-ol

25 m-Anisidine (12.6 g, 0.102 moles) and ethyl dithioacetate (12.3 g, 0.102 moles) were combined with vigorous stirring and heated to about 65°C while flushing slowly with N₂(g). After 5 hours, additional ethyl dithioacetate (1.0 g) was added and stirring under N₂(g) at ambient temperature was continued. The mixture was diluted with EtOAc (200 mL) and the organic solution was washed with 1N HCl (3 x 50 mL), and brine (50 mL), dried over MgSO₄, filtered and concentrated in vacuo to provide a dark yellow solid (13.2 g). This thioamide may be used directly for the following reaction or chromatographed to purity on silica (5-20% EtOAc/hexanes).

30 A mixture of the thioamide from above (1.00 g, 5.52 mmol) and NaOH (1.63 g, 40.8 mmol) dissolved in H₂O (25 mL) and MeOH (2 mL) was added dropwise with stirring to a partial suspension of K₃Fe(CN)₆ (6.0 g, 18.2 mmol) in H₂O (15 mL) at about 60°C. The mixture was stirred for 2 hours at about 60°C and then K₂CO₃ (4.0 g, 29 mmol) was added and stirring was continued for 1 hour at 50-60°C. After cooling to

-97-

room temperature the mixture was extracted with Et_2O (3 x 25 mL), and the organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue (800 mg) was chromatographed on silica to separate the less polar 7-methoxy-2-methyl-benzothiazole
5 (440 mg, 44%) from the 5-methoxy isomer.

7-Methoxy-2-methyl-benzothiazole (400 mg, 2.23 mmol) was mechanically mixed with solid pyridine hydrochloride (6.00 g, 52 mmol) and then heated to 160-170°C in a sealed vessel for 16 hours. Water (40 mL) was added to the warm mixture, the pH was adjusted to neutrality with NaHCO_3 and the mixture was extracted with 1:1
10 $\text{CHCl}_2/\text{CHCl}_3$ (4 x 10 mL). The pooled organic extracts were dried over MgSO_4 , filtered, and concentrated in vacuo to provide 2-methyl-benzothiazol-7-ol as a waxy yellow solid.
(260 mg; GC-MS m/z 165).

Preparation 2

2-(Pyridin-2-yl)benzothiazol-7-ol and 2-(pyridin-2-yl)benzothiazol-5-ol

15 The title compounds were prepared as described by T. Hisano, M. Ichikawa, K. Tsumoto and M. Tasaki in Chem. Pharm. Bull. 30, 2996-3004 (1982). m-Anisidine (28.1 mL, 0.25 mol), 2-picoline (24.7 mL, 0.25 mol) and sulfur (20.1 g) were heated under $\text{N}_2(\text{g})$ atmosphere to about 170°C for about 10 h. After cooling EtOH (500 mL) was added and the mixture was refluxed for 30 min. and concentrated in vacuo. The
20 resulting yellow solid residue was extracted with 10% aqueous KOH (500 mL). Upon cooling the KOH extract to about 20°C, the 5-methoxy-2-(pyridin-2-yl)-benzothiazole crystallized. This material was recovered by filtration, pooled with hot KOH-insoluble solids, and recrystallized from EtOH (19.6 g; m.p. 132-134°C; GC-MS m/z 242) before demethylation to the 2-(pyridin-2-yl)benzothiazol-5-ol (18.2 g; m.p. 267-273°C; GC-MS
25 m/z 228) utilizing pyridine-HCl at about 170°C as described in Preparation 1.

30 The aqueous KOH filtrate was neutralized with 3N HCl causing the thioanilide to separate. This material was recovered by extraction into EtOAc . Organic phases were dried over $\text{Na}_2\text{SO}_4(\text{s})$ and concentrated in vacuo to afford ~6.5 g of crude thioamide which was oxidatively cyclized to a mixture of the 5-methoxy and 7-methoxy-2-(pyridin-2-yl)benzothiazoles with $\text{K}_3\text{Fe}(\text{CN})_6$ as outlined in Preparation 1 above. The reaction mixture was extracted with CHCl_3 (4 x 50 mL), and pooled extracts were dried over $\text{Na}_2\text{SO}_4(\text{s})$ before concentrating in vacuo. The residue was flash chromatographed on silica using 25% $\text{EtOAc}/\text{hexanes}$ to separate the 7-methoxy isomer (330 mg; GC-MS m/z 242) from the 5-methoxy isomer. Demethylation was again performed utilizing
35

pyridine·HCl at about 170°C to afford 2-(pyridin-2-yl)benzothiazol-7-ol (274 mg; GC-MS m/z 228).

Preparation 3

5

7-Hydroxybenzothiazole

The title compound was prepared as a mixture (60/40) with the 5-hydroxy isomer in the deprotection of 2-carbamoyl-7-methoxybenzothiazole (obtained in Preparation 4 below) with pyridine·HCl, according to the method described in Preparation 1. The mixture of the 5- and 7-hydroxybenzothiazoles was used directly in the preparation of 10 the isomeric glycidyl ethers which were readily separable by chromatography on silica (2% CH₃CN/CH₂Cl₂).

Preparation 4

2-Cyano-7-hydroxybenzothiazole and 2-Carbamoyl-7-hydroxybenzothiazole

The title compounds were prepared according to the method of E. H. White and 15 H. Wörther, J. Org. Chem. 31, 1484-1488 (1966). A solution of KOH (12.2g) in EtOH (40 mL) was saturated with H₂S(g) and an equal volume of KOH (12.2 g) in EtOH (40 mL) was added. To this solution in a 500 mL round-bottomed flask equipped with a reflux condenser was added trichloroacetamide (15.0 g, 92.4 mmol) in EtOH (80 mL). Following the ensuing exothermic reaction the deep red solution was warmed to about 20 50°C for about 20 min., cooled to about 20°C and a freshly prepared neutralized (with K₂CO₃) solution of chloroacetic acid in H₂O (80 mL) was added. After 30 min., the deep red solution of carbamoylthiocarbonylthioacetic acid was filtered to remove precipitated KCl(s), and *m*-anisidine (7.54 mL) was added to the filtrate. The mixture was stirred at about 20°C for about 4 1/2 days with a slow flush of N₂(g) through the 25 vessel (H₂S(g) evolved). The solution was concentrated in vacuo to 200 mL, H₂O (400 mL) was added, and the mixture was warmed to dissolve all materials. Slow cooling to about 20°C afforded 3-methoxythioxanilamide (4.5 g, m.p. 135°C) as yellow needles. This material (4.48 g, 21.3 mmol) was dissolved in H₂O (100 mL) with NaOH (6.30g) and added dropwise with stirring at about 20°C to K₃Fe(CN)₆ (23.1 g) in H₂O (60 mL). After about 2 h the reaction mixture was cooled to about 10°C for about 30 min., and the brown precipitate containing a 1:1 mixture of 2-carbamoyl-5- and 7-methoxybenzo-thiazoles (1.96 g) was recovered by filtration, and used below (and in Preparation 3) without further purification. This product (1.46 g, 7.0 mmol) was dissolved in dry pyridine (27 mL), cooled to about -10°C and treated dropwise over 30 about 10 min. with POCl₃ (1.7 mL). After stirring for about 2 h at about 20°C, 35

-99-

cyclohexane (215 mL) was added followed by H₂O (150 ml). Phases were separated and the aqueous phase was washed with cyclohexane (3 x 80 mL). Organic phases were pooled, dried over MgSO₄(s) and concentrated to afford a yellow oily solid (1.19 g) which was flash chromatographed on silica (25% acetone/hexanes) to afford a yellow crystalline solid (1.09 g) containing a 1:1 mixture of 2-cyano-5-methoxybenzothiazole and the 7-methoxy isomer. This material was demethylated using pyridine-HCl at about 180°C for about 6 h as described in Preparation 1 and the recovered products were flash chromatographed on silica (2% CH₃CN/CH₂Cl₂) to afford 2-cyano-7-hydroxybenzothiazole (448 mg, m.p. 225°C) as the first eluting isomer and 2-cyano-5-hydroxybenzothiazole (370 mg, m.p. 194°C) as the later.

Preparation 5

4-Hydroxy-2,1,3-benzothiodiazole

4-Amino-2,1,3-benzothiodiazole (5.00 g, 33.0 mmol) was added to a solution of KHSO₄ (92.1 g, 0.676 moles) in H₂O (120 mL) at about 100°C followed by NaHSO₃ (24.0 g, 0.231 moles). When the vigorous bubbling ceased, the solution was brought to reflux under N₂(g) for 72 hours. The mixture was cooled to about 22°C, the pH was adjusted to 7-8, and the volume of the mixture was increased to 500 mL to dissolve the salts. Multiple extractions with 1:1 CHCl₃/CH₂Cl₂ (7 x 150 mL), followed by drying of the organic phases over Na₂SO₄ and concentration in vacuo afforded a reddish-brown residue (4.51 g; >90% purity) which was chromatographed on silica in 20→30% acetone/hexane, to yield 3.90 g of pure product.

Preparation 6

2-Methylamino-3-nitrophenol

The title compound was prepared from 2-amino-3-nitrophenol according to a procedure adapted from Tet. Lett. 23, 3315 (1982). 2-Amino-3-nitrophenol (7.7 g, 50 mmol) in dry THF (20 mL) was treated dropwise with formic-acetic anhydride (130 mmol) in THF (10 mL) at about -5°C under N₂(g). After stirring 3 hours the mixture was concentrated in vacuo to a viscous oil which was redissolved in THF (12 mL) and treated dropwise with 2M borane-dimethylsulfide in THF (63 mL) at about -5°C. When the addition was complete the mixture was heated to reflux (2 hours), cooled in ice and quenched with MeOH (20 mL). After stirring for 1 hour at about 22°C, anhydrous HCl was bubbled into the solution to acidity it to about pH 2. The mixture was refluxed for 1 hour and concentrated in vacuo. The residue was dissolved in H₂O, neutralized with conc. NH₄OH and cooled (16 hours) to produce a dark brown solid. This wet material

-100-

was dissolved in CHCl_3 , dried over Na_2SO_4 and concentrated in vacuo to afford a red-brown solid (6.72 g; >95% purity) which was used directly in the syntheses of 3-methylbenzimidazol-4-ol and 3-methylbenzotriazol-4-ol (below).

5

Preparation 7

3-Methyl-1,2,3-benzotriazol-4-ol

2-Methylamino-3-nitrophenol (2.50 g, 14.9 mmol) in MeOH (200 mL) with HOAc (0.5 mL) was hydrogenated (40 psi, 2 hours) in the presence of 10%Pd on carbon (250 mg). Following removal of the catalyst by filtration the solution was concentrated in vacuo. The residue was resuspended in H_2O (30 mL), and 3N HCl (10 mL) was added dropwise while stirring at 0-5°C, immediately followed by 1.1M NaNO_2 (15 mL, 16.5 mmol) in H_2O dropwise over 20 minutes. After 30 minutes at about 22°C, the mixture was recooled to about 5°C, and the pH adjusted to about 6 with conc. NH_4OH . The resulting solution was extracted with EtOAc (3 x 20 mL). The pooled organic extracts were dried over Na_2SO_4 and concentrated to yield a dark red-brown solid (2.23 g) which was chromatographed on silica (50→90% $\text{EtOAc}/\text{hexanes}$) to afford 1.26 g of pure product as a tan solid (GC/MS m/z 149).

Preparation 8

3-Methyl-3H-benzoimidazol-4-ol

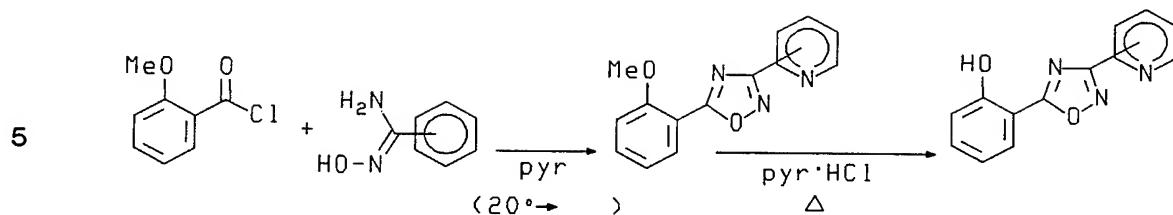
20 2-Methylamino-3-nitrophenol (1.00 g, 5.98 mmol) in MeOH (100 mL) with HOAc (0.22 mL) was hydrogenated (50 psi) for 2 hours over 10% Pd on carbon (186 mg). The catalyst was removed by filtration and the filtrate concentrated in vacuo. The residue was dissolved in formic acid and refluxed for 17 hours under $\text{N}_2(\text{g})$. Excess acid was removed in vacuo, and the residue was taken up in 5% MeOH in EtOAc and washed with saturated aqueous NaHCO_3 and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was taken up in 5% MeOH in EtOAc and washed with saturated aqueous NaHCO_3 and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to yield a red-brown solid which was chromatographed on silica (50 - 100% $\text{EtOAc}/\text{hexanes}$). The desired product (GC/MS 30 m/z 148) was obtained as a yellow solid, 0.748 g; 84%.

Preparation 9

2-,3- or 4-[(5-Pyridinyl)-[1,2,4]oxadiazol-3-yl)]phenols

The 2- and 4-pyridoaminoximes were prepared from the corresponding cyanopyridines and hydroxylamine described for 3-pyridoaminoxime in Preparation 58 below. The 2-, 3- and 4-[3-(2-methoxyphenyl)-[1,2,4]oxadiazol-5-yl] pyridines were

-101-



prepared by reaction of the appropriate pyridoaminoxime with α -anisoyl chloride in 10 pyridine ($20^{\circ}\text{C} \rightarrow$ reflux) according to Preparation 62 below. Deprotection to yield the 2-, 3- or 4-(5-pyridinyl-[1,2,4]oxadiazol-3-yl)phenol was effected by heating a mixture of the methoxy derivative (from above) with 10 parts pyridine-HCl(s) at about 160°C for 6-16 hours. The melt was poured into H_2O (100-150 parts) with stirring and the precipitated product was filtered and dried in vacuo.

15

Preparation 10

2-(Oxazol-2-yl)-phenol

2-Benzylbenzamide (2.0 g, 8.8 mmol) was heated to about 130°C in bromoacetaldehyde dimethylacetal (10 mL, 85 mmol) under $\text{N}_2(\text{g})$ for 3.5 hours. Although pure 2-(2-benzylphenyl)oxazole could be obtained by recrystallization from 20 $\text{CHCl}_3/\text{CCl}_4$, the entire mixture was usually directly hydrogenated using 10% Pd on carbon (600 mg) at 40 psi of H_2 in 1% HOAc in MeOH (100 mL). Following removal of catalyst by filtration and concentration of the filtrate in vacuo the residue was chromatographed on silica (10 \rightarrow 15% acetone/hexanes) to afford 2-(oxazol-2-yl)phenol (860 mg; GC-MS m/z 161 (M^+)).

25

Preparation 11

2-(Thiazol-2-yl)phenol

The title compound was prepared according to the method in Z. Naturforsch. 376, 877-880 (1982) or Helv. Chim. Acta 36, 886-890 (1953). α -Cyanophenol (55 mmol, 6.55 g) in EtOAc (160 mL) was treated with diethyl dithiophosphate (9.15 mL, 55 mmol) and 30 HCl(g) was bubbled into the stirred solution at a moderate rate for about 45 min. without external cooling. After stirring at about 20°C under $\text{N}_2(\text{g})$ for about 16 h., excess HCl was removed by $\text{N}_2(\text{g})$ sparge and saturated aqueous Na_2CO_3 (100 mL) was added carefully with stirring. The organic phase was separated and washed (3x) with saturated Na_2CO_3 until no further orange color resulted in the aqueous phases. 35 The organic phase was dried over $\text{Na}_2\text{SO}_4(\text{s})$ and concentrated in vacuo. An orange

-102-

5 crystalline impurity (~ 3.0 g; m.p. 215°C, EI-MS m/z 255) precipitated upon addition of ether and was removed by filtration. The filtrate was concentrated in vacuo and recrystallized from Et₂O/hexanes to afford 2.9 g (m.p. 117°C; GC-MS m/z 153) of the
10 desired thioamide. This material (2.0 g, 13 mmol) was dissolved in EtOH (5 mL) and α-bromoacetaldehyde dimethyl acetal (1.55 mL, 13 mmol) was added. The mixture was refluxed under N₂(g) atmosphere for 3.5 h. and Et₂O (15 mL) was added to complete the precipitation of the 2-(thiazol-2-yl)phenol as its hydrobromide salt which was recrystallized from MeOH/CHCl₃/Et₂O to produce 1.55 g of pure HBr salt (LSIMS m/z 178 (MH⁺)). This material could be alkylated directly if an extra equivalent of base was included to neutralize the HBr, or it could be free-based by extraction from saturated aqueous NaHCO₃ with Et₂O followed by drying over Na₂SO₄(s) and concentration of etheral phases in vacuo.

Preparation 12

15 2-(Thiazol-4-yl)phenol

20 *o*-(Bromoacetyl)phenyl acetate (5.0 g, 19.5 mmol) was treated with crude thioformamide (filtrate concentrated in vacuo from reaction of P₂S₅ (1.1 eq.) and (25 mmol) formamide in THF (30-40°C, 5 hours)) in refluxing acetone (60 mL). After 16 hours the reaction mixture was cooled to about 10°C and the precipitated HBr salt of 2-(thiazol-4-yl)phenol was recovered. 31%, 1.50 g, LSIMS m/z=178 (MH⁺).

Preparation 13

2-(2-Methylthiazol-4-yl)phenol

25 The title compound was prepared according to the method described in Preparation 12 but utilizing pure thioacetamide rather than crude thioformamide. Yield: 65% as the HBr salt; LSIMS m/z 192 (MH⁺).

Preparation 14

2-[2-(Pyridin-3-yl)thiazol-4-yl]phenol

30 *o*-(Bromoacetyl)phenyl acetate (2.57 g, 10 mmol) in dry acetone (30 mL) was treated with thionicotinamide (1.38 g, 10 mmol). The mixture was refluxed 16 hours, cooled to about 20°C at which point a precipitate formed (2.46 g). The precipitate was filtered and dried in vacuo. The precipitate was dissolved in MeOH (50 mL) and treated with 10% NaOH in H₂O (20 mL) for 1 hour at about 20°C to hydrolyze the acetate ester. The pH was adjusted to neutrality with 6N HCl while chilling on ice/H₂O and the volume was reduced to about 35 mL in vacuo. After cooling to about 4°C, an orange solid

-103-

precipitate formed, which was removed by filtration and dried in vacuo to constant mass to yield 36-50% product (LSIMS m/s 254 (M⁺)).

Preparation 15

5

2-[(Thiazol-2-yl)oxy]phenol

o-Benzylxyphenol (7.5 g, 37.5 mmol) in dry DMF (60 mL) was treated with Me₄N⁺OH·5H₂O (37.5 mmol, 6.8 g) followed by 2-bromothiazole (6.15 g, 37.5 mmol). The stirred solution was heated to about 100°C under N₂(g) for 16 hours. The mixture was cooled in ice and crystalline, H₂O-soluble Me₄N⁺Br was removed by filtration. The 10 filtrate was concentrated in vacuo and partitioned between Et₂O (100 mL) and H₂O (60 mL). The organic phase was washed with 1N NaOH (3x) and brine, dried over Na₂SO₄ and concentrated in vacuo to afford 4.9 g of crude 2-(2-benzylxyphenyl)thiazole (GCMS m/z 283 (M⁺)). This material was directly deprotected by treatment with 33% HBr in HOAc (35 mL) for 2 hours at about 20°C.

15

The solution was poured onto ice/H₂O (300 mL) and the pH adjusted to neutrality by addition of conc. NH₄OH. The product was extracted into EtOAc/Et₂O (1:2) (250 mL) and the organic extract was washed with brine, dried over Na₂SO₄ and concentrated in vacuo to an oil. 2-[(Thiazol-2-yl)oxy]phenol was obtained as its HCl salt by precipitation from Et₂O upon dropwise addition of 1N HCl in Et₂O (15mL). 2.25 20 g, 27% overall; GC-MS m/z 193 (M⁺).

Preparation 16

3-[(Thiazol-2-yl)oxy]phenol

3-Methoxyphenol (2.48 g, 20 mmol), 2-bromothiazole (3.28 g, 20 mmol) and Me₄N⁺OH·5H₂O (3.62 g, 20 mmol) were heated in dry DMF (30 mL) under N₂(g) for 16 25 hours. The mixture was filtered and the filtrate was partitioned between H₂O and EtOAc. Organic extracts were pooled, dried over Na₂SO₄ and concentrated in vacuo. The residue was chromatographed on silica (CHCl₃) to yield 2.51 g of 2[(3-methoxyphenyl)oxy]thiazole (GC-MS m/z 207 (M⁺)). A portion (2.42 g, 11.7 mmol) of this material was dissolved in dry CH₂Cl₂ (40 mL), and BBr₃ (2.2 eq.) was added 30 dropwise at about -10°C under N₂(g). The mixture was allowed to warm to about 20°C, stirred 3 hours, and then poured into ice/H₂O and extracted with CH₂Cl₂. Organic extracts were washed with 5% NaHCO₃ and brine, dried over Na₂SO₄ and concentrated in vacuo to yield 3-[(thiazol-2-yl)oxy]phenol as an oil (1.3 g) which was used without further purification (GC-MS m/z 193 (M⁺)).

-104-

Preparation 17

2-[(Thiazol-2-yl)thio]phenol

To 2-methoxybenzenethiol (2.8 g, 20 mmol), and 2-bromothiazole (3.29 g, 20 mmol) in dry DMF (30 mL) under N₂(g) was added Me₄N⁺OH⁻·5H₂O (3.62 g, 20 mmol).
5 The stirred mixture was heated to about 100°C for 16 hours. Isolation of the methoxyphenyl intermediate, and its subsequent deprotection to the desired product with BBr₃ was accomplished according to the method described in Preparation 16 (yield 81%; GC-MS m/z 209).

Preparation 18

2-[(Imidazol-2-yl)methyl]-phenol

A mechanical mixture of imidazole (5 eq., 3.5 g) and 2-hydroxybenzyl alcohol (1.0 eq., 1.24 g) was heated to about 120°C in a stoppered flask. The melt was stirred for 5 hours at about 120°C, allowed to cool and the fused mass was treated with hot H₂O (40 mL) and the resulting suspension was cooled to about 4°C. The white 15 crystalline precipitate was filtered and dried in vacuo to constant mass (1.49 g, 85%; LSIMS m/z 175 (MH⁺)).

Preparation 19

2-(Imidazol-1-yl)phenol

To a mixture of oxazole (2.39 g, 34 mmol) and *o*-anisidine (69 mmol, 8.6 g) at 20 about 20°C was added TsOH·H₂O (50 mg, 0.008 eq.) and the stirred mixture was gradually heated to reflux in a 160° oil bath over 30 minutes under N₂(g). After 5 hours at about 160°C most of the excess *o*-anisidine and N-formyl *o*-anisidine by-product were removed by vacuum distillation at about 160°C (5 mm→0.5 mm Hg). The residue 25 was partitioned between 1N HCl and EtOAc. The acidic aqueous phase was washed with CH₂Cl₂, the pH of the aqueous phase was adjusted to 10, and the 1-(2-methoxyphenyl)imidazole extracted into EtOAc. Passage through a filtration column of silica (40→65% acetone/hexane) afforded the pure methoxy intermediate (8.75 mg). The above compound was deprotected by addition of BBr₃ (2.0 eq.) to a CH₂Cl₂ solution 30 (15 mL) of the imidazole at about -78°C followed by warming and stirring 16 hours at about 20°C. The mixture was quenched with H₂O (10 mL), and the pH of the aqueous phase adjusted to 7.5 with saturated aqueous NaHCO₃, and this phase was saturated with NaCl. Extractions with CH₂Cl₂ (2x) and EtOAc (2x), followed by drying of the pooled organic phases over Na₂SO₄ and concentration in vacuo afforded 1.05 g of a

-105-

solid which was recrystallized from MeOH to produce pure 2-(Imidazol-1-yl)phenol as a tan solid (63%; GC-MS m/z 160 (M⁺)).

Preparation 20

5

2-[1,3,4]Oxadiazol-2-yl)phenol

Salicyl hydrazide (7.6 g, 50 mmol) was heated to reflux in triethyl orthoacetate (40 mL) for 20 hours. Upon cooling to about 0°C the product crystallized, and was recovered by decanting the excess triethyl orthoacetate, suspending the moist solid in cold EtOH (25 mL), filtering and drying in vacuo (4.43 g, 51%).

10

Preparation 21

1-(2-Methoxybenzoyl)-2-(nicotinoyl)hydrazide

To 2-Methoxybenzoyl hydrazide (7.0 g, 42 mmol) slurried in dry THF (10 mL) was added pyridine (3.0 eq., 126 mmol, 10 g) followed by nicotinoyl chloride hydrochloride (7.5 g, 42 mmol). Immediately product began to precipitate and after 15 stirring 2.5 hours at about 20°C, the solids were filtered, washed with Et₂O and dried in vacuo to yield 81% (9.23 g) of product.

Preparation 22

3-[2-(2-Methoxyphenyl)-[1,3,4]oxadiazol-5-yl]pyridine

1-(2-Methoxybenzoyl)-2-(nicotinoyl)hydrazide (2.0 g; 7.37 mmol) from above and 20 DMF-SO₃ complex (4.52 g, 29.5 mmol) were stirred in dry DMF (20 mL) at about 80°C for 2 hours. The reaction mixture was poured into H₂O (100 mL) and extracted with Et₂O (5 x 20 mL). The pooled organic extracts were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to afford product (1.66 g, >95% pure) which was directly deprotected.

25

Preparation 23

2-(5-Pyridin-3-yl-[1,3,4]oxadiazol-2-yl)phenol

The methoxy derivative from Preparation 22 (0.80 g, 3.16 mmol) was mixed with solid pyridinium hydrochloride (9.12 g, 79 mmol) and heated to about 170°C for 4 hours. H₂O (20 mL) was added and the pH was adjusted to 7-8 with 6N NaOH. The 30 aqueous mixture was extracted with EtOAc and CH₂Cl₂, and the pooled organic extracts were dried over Na₂SO₄, concentrated and chromatographed on silica (20-25% acetone/hexanes) to afford 43% (329 mg) product.

-106-

Preparation 24

3-[2-(2-Methoxyphenyl)-[1,3,4]thiadiazol-5-yl]pyridine

To a slurry of 1-(2-methoxybenzoyl)-2-(nicotinoyl)hydrazide (4.0 g, 14.8 mmol
5 from Preparation 22) in anhydrous toluene (50 mL) was added Lawesson's reagent (2.0 eq., 29.6 mmol, 12.0 g). The stirred mixture was heated to reflux under N₂(g) for 16 hours. The cooled (20°C) reaction mixture was filtered and the residue was washed with CH₃CN and CH₂Cl₂. The pooled filtrate and washes were concentrated in vacuo
10 and chromatographed on silica (35% acetone/hexanes) to afford 85-90% product (3.5 g; LSIMS m/z 270 (MH⁺)).

Preparation 25

2-(5-Pyridin-3-yl-[1,3,4]thiadiazol-2-yl)phenol

The methoxy derivative from preparation 24 (3.6 g) was deprotected by heating with pyridinium hydrochloride (20 g) at about 170°C for 16 hours as described in
15 Preparation 24 to afford 1.1 g product 32%; LSIMS m/z 255 (MH⁺) after chromatography of the extracts on silica (0→2% MeOH/CH₂Cl₂).

Preparation 26

2-(5-Pyridin-4-yl-[1,3,4]thiadiazol-2-yl)phenol

This product was prepared as outlined for the pyridin-3-yl analog of Preparations
20 24 and 25 but utilizing isonicotinoyl chloride with 2-methoxybenzoyl hydrazide in the initial formation of the diacyl hydrazide.

Preparation 27

Potassium dithioformate

KOH (12 g) in MeOH (45 mL) was saturated with H₂S(g) at about 5°C. A
25 solution of KOH (11 g) in MeOH (35 mL) was added to this solution in a 500 mL round-bottom flask equipped with a reflux condenser. The solution was warmed to about 50°C and CHCl₃ (15 g) was added. After the exothermic reaction subsided the red-orange mixture was stirred for 10 minutes at about 50°C, then cooled in ice/H₂O and precipitated KCl(s) was removed by filtration and washed with MeOH. The pooled
30 filtrate and washings containing about 33 mmol potassium dithioformate were concentrated to approximately 50 mL and used immediately in subsequent reactions.

Preparation 28

2-[1,3,4]Thiadiazol-2-yl)phenol

35 Salicyl hydrazide (33 mmol, 5.0 g) was added to the methanolic solution of potassium dithioformate (about 33 mmol in 50 mL from preparation 27) along with H₂O

-107-

(40 mL). The mixture was stirred for 24 hours under N₂(g), diluted to 150 mL with H₂O and neutralized with HOAc (with evolution of H₂S(g)) to produce a precipitate of 2-(2-hydroxybenzoyl)-1-thioformyl hydrazide (6.5 g, 100%) which was filtered and dried. This
5 material (5.8 g) was directly cyclized by addition in small portions to stirred conc. H₂SO₄ (30 mL) at about 20°C. After 30 minutes the solution was poured onto ice (150 mL) and neutralized with con. NH₄OH with cooling on ice/H₂O to precipitate 2-([1,3,4]thiadiazol-2-yl)phenol (2.12 g; GC-MS m/z 178).

Preparation 29

10 3-([1,3,4]Thiadiazol-2-yl)phenol

This product was prepared in a manner analogous to that for 2-([1,3,4]thiadiazol-2-yl)phenol of Preparation 28 but utilizing 3-hydroxybenzoyl hydrazide (2.5 g, 16.5 mmol), 2.58 g product was isolated.

Preparation 30

15 2-(5-Methyl-[1,3,4]thiadiazol-2-yl)phenol

To acetyl hydrazide (9.9 g, 50 mmol) in anhydrous pyridine (60 ml) at 0-5°C was added o-acetylsalicyl chloride (9.93 g, 50 mmol). The solution was stirred 4 hours at about 20°C, and P₂S₅ (15 g) was added. The resulting mixture was heated to near boiling within 10 minutes at which point all of the P₂S₅ dissolved. After 40 minutes the
20 mixture had cooled and was then heated in a bath at about 100°C for 16 hours. EtOH (60 mL) was added and the mixture was poured into H₂O (800 mL) and stirred for 30 minutes. The pH of the stirred mixture under N₂(g) was raised to about 11 and maintained by addition of 6N NaOH. After 1 hour at about 20°C the pH was adjusted to 6-7 by addition of 6N HCl, and the mixture extracted with EtOAc. Organic extracts
25 were pooled, dried over Na₂SO₄(s), concentrated and flash chromatographed on silica (10→15% acetone/hexanes) to yield the desired product as a beige solid (950 mg, 10%; LSIMS m/z 193 (MH⁺)).

Preparation 31

30 3-(5-Phenyl-[1,3,4]thiadiazol-2-yl)phenol

3-Hydroxybenzoyl hydrazide (3.6 g, 23.5 mmol) was added to 5-(thiobenzoyl)-thioglycolic acid (5.0 g, 23.5 mmol) in 1N NaOH (24 mL) with H₂O (10 mL) and MeOH (10 mL). After stirring 16 hours at about 20°C the mixture was filtered, and the residue of 1-thiobenzoyl-2-(3-hydroxybenzoyl)hydrazide (LSIMS m/z 273) was washed with H₂O and dried briefly. This material was cyclized in conc. H₂SO₄ as described for the 2-
35

-108-

([1,3,4]thiadiazol-2-yl)phenol analog of Preparation 28 to afford 85% product (4.57 g; LSIMS m/z 255 (MH⁺)).

Preparation 32

5

2-(Dimethylamino)benzothiazol-7-ol

To m-anisidine (12.32 g, 0.1 mol) and triethylamine (1.2 eq, 0.12 mol, 16.7 mL) in CH₂Cl₂ (100 mL) was added a 1M solution of dimethylthiocarbamyl chloride in CH₂Cl₂ (100 mL, 0.10 mol) with stirring at about 0°C for about 5 minutes. The solution was allowed to warm to about 22°C and stirred for about 16 hours under N₂(g). The 10 mixture was concentrated in vacuo to a syrup, H₂O (250 mL) was added and the mixture was stirred for about 1 hour at about 40-50°C. Concentrated HCl (50 mL) was added and the mixture was extracted with Et₂O (3 x 200 mL). The etheral phases were washed with 2N HCl (3 x 150 mL), H₂O (100 mL), and saturated NaHCO₃ (100 mL), and dried over Na₂SO₄(s). Concentration in vacuo afforded a brown solid which was 15 recrystallized from CHCl₃/Et₂O/hexanes to provide pure thiourea (8.6 g). Additional thiourea (4.1 g) crystallized from the acidic aqueous phases on standing for several days.

A mixture of the thiourea from above (4.46 g, 21 mmol) and NaOH (6.3 g, 156 mmol) in MeOH (25 mL)/H₂O (80 mL) was added dropwise with stirring to a solution of 20 K₃Fe(CN)₆ (23.0 g, 70 mmol, 3.3 eq) in H₂O (60 mL) at about 60-65°C over about 15 minutes. The mixture was stirred for about 2 hours at about 60°C and then K₂CO₃(s) (16 g) was added. The stirred mixture was allowed to cool and then extracted with Et₂O (2 x 100 mL) and CHCl₃ (1 x 80 mL). Pooled organic extracts were dried over 25 Na₂SO₄(s), and concentrated in vacuo onto 20 g of silica and flash chromatographed using 15→30% acetone/hexanes to afford 1.6 -2.2 g (37-50%) of 2-(dimethylamino)-7-methoxybenzothiazole.

The 7-methoxy derivative from above (800 mg, 3.8 mmoles) was mechanically mixed with pyridinium hydrochloride (11.2 g, 0.10 mol) and heated to about 160°C for about 18 hours. The mixture was poured onto ice/H₂O and stirred for about 10 min. 30 and then extracted with CHCl₃ (5 x 50 mL). Pooled organic phases were dried over Na₂SO₄(s), filtered and concentrated in vacuo to afford 730 mg (98%) of 2-(dimethylamino)benzothiazol-7-ol as a grey solid (GC-MS m/z 194) which was used without further purification.

Preparation 332-(Pyridin-3-yl)benzothiazol-7-ol

To a stirred solution of m-anisidine (50 mmol, 5.62 mL, 6.16 g) in 2:1 THF/H₂O (75 mL) with NaHCO₃(s) (8.4 g, 0.1 mol) was added nicotinoyl chloride hydrochloride (50 mmol, 8.9 g) in small portions over about 5 min. at about 20°C. The mixture was stirred under N₂(g) for about 20 hours and then saturated aqueous NaHCO₃ (60 mL) and Et₂O (75 mL) were added. The organic phase which separated was washed with saturated aqueous NaHCO₃ (3 x 30 mL), and brine (1 x 30 mL), dried over Na₂SO₄(s) and concentrated in vacuo. The solid residue was recrystallized from Et₂O/petroleum ether to afford 8.65 g of the nicotinamide. This product (5.0 g, 21.9 mmol) was suspended in dry toluene (100 mL) with Lawesson's reagent (17.1 g, 42.3 mmol) and heated to reflux under N₂(g) for about 16 hours. After cooling to about 20°C the mixture was filtered and the residue was washed with anhydrous THF (2 x 50 mL). Pooled filtrate and washings were concentrated in vacuo, stirred vigorously in i-PrOH (100 mL) and saturated NaHCO₃ (250 mL) at about 50°C for about 90 min., cooled and extracted into CHCl₃ (2 x 200 mL). The oily residue obtained after drying the extract over Na₂SO₄(s) and concentration in vacuo was flash chromatographed on silica using a 50→60% acetone/hexanes gradient to yield 3.1 g of pure nicotinoylthioamide.

The thioamide (2.44 g, 101 mmol) from above was suspended in a mixture of MeOH (40 mL) and aqueous NaOH (3.2 g in 100 mL H₂O) and added dropwise over 10 min. to a solution of K₃Fe(CN)₆ (11.5 g) in H₂O (40 mL) at about 60°C. After stirring for about 2 hours at about 60°C additional K₃Fe(CN)₆ (6 g) was added and stirring at about 60°C was continued for about another 1 hour. K₂CO₃(s) (8.2 g) was added at about 60°C and the stirred mixture was allowed to cool about 30 min. before extracting with Et₂O (3 x 80 mL). Pooled organic extracts were dried over MgSO₄(s), filtered and concentrated to give 2.1 g of an oil which was flash chromatographed on silica (35→40% EtOAc/hexanes) to afford pure 7-methoxy-2-(pyridin-3-yl)benzothiazole (0.67 g). This material was O-demethylated using molten pyridinium hydrochloride as previously described in Preparation 32 to yield 2-(pyridin-3-yl)benzothiazol-7-ol. LC-MS m/z 229 (MH⁺); Analytical RP-HPLC, 3.10 min.

Preparation 342-Methyl-benzoxazol-6-ol

4-Aminoresorcinol hydrochloride (2.0 g, 12.4 mM), acetyl chloride (1.0 g, 12.6 mM), triethylamine (1.38 g, 13.6 mM) and pyridinium-p-toluenesulfonate (PPTS, 800

-110-

mg, 3.2 mM) were refluxed in xylenes (50 mL) for about 18 hours. Additional PPTS (300 mg) was added and the mixture was then refluxed about 48 hours. The reaction mixture was concentrated and the residue dissolved in ethyl acetate (200 mL) and 5 washed with H₂O (3 x 150 mL). The combined aqueous layer was back extracted with ethyl acetate (200 mL) and the combined organic layers were dried over MgSO₄. Filtration and concentration provided 1.36 g. Filtration through a silica gel column eluted with 10% methanol/methylene chloride provided an orange solid, 0.3 g; m.p., 94-96°C.

Preparation 35

10

2-(Pyridin-2-yl)-benzoxazol-6-ol

15

4-Aminoresorcinol hydrochloride (2.0 g, 12.4 mL), picolinyl chloride hydrochloride (2.4 g, 13.6 mM), triethylamine (2.8 g, 27.2 mM) and pyridinium-p-toluenesulfonate (PPTS, 800 mg, 3.2 mM) were refluxed in xylenes (50 mL) for about 72 hours. The reaction mixture was concentrated and the residue dissolved in ethyl acetate (200mL) and washed with H₂O (3 x 150 mL). The combined aqueous layer was back extracted with ethyl acetate (200 mL) and the combined organic layer was dried over MgSO₄. Filtration and concentration provided 1.0 g. Filtration through a silica gel column eluted with 4% methanol/methylene chloride provided an orange solid, 0.32 g; m.p., 100-103°C.

20

Preparation 36

25

2-(Pyridin-3-yl)-benzoxazol-6-ol

2-Pyridin-3-yl-benzoxazol-6-ol was prepared using 4-aminoresorcinol hydrochloride (1.5 g, 9.3 mM), nicotinyl chloride hydrochloride (1.8 g, 10.2 mM), triethylamine (3.0 g, 30.0 mM) and pyridinium-p-toluenesulfonate (PPTS, 800 mg, 3.2 mM) were refluxed in xylenes (50 mL) for about 24 hours as described for 2-pyridin-2-yl-benzoxazol-6-ol; m.p., 176-178°C.

Preparation 37

2-(Pyridin-4-yl)-benzoxazol-6-ol

30

2-Pyridin-4-yl-benzoxazol-6-ol was prepared using 4-aminoresorcinol hydrochloride (1.5 g, 9.3 mM), isonicotinyl chloride hydrochloride (1.8 g, 10.2 mM), triethylamine (3.0 g, 30.0 mM) and pyridinium-p-toluenesulfonate (PPTS, 800 mg, 3.2 mM) were refluxed in xylenes (50 mL) for about 24 hours as described for 2-pyridin-2-yl-benzoxazol-6-ol; m.p., 139-143°C.

-111-

Preparation 38

Benzoxazol-6-ol

4-Aminoresorcinol hydrochloride (3.0 g, 18.5 mM), triethylorthoformate (9.1 g, 5 61.4 mM), and pyridinium-p-toluenesulfonate (PPTS, 250 mg, 1.0 mM) were refluxed in xylenes (200 mL) for about 18 hours. The reaction mixture was concentrated and the residue dissolved in ethyl acetate (200 mL) and washed with H₂O (3 x 150 mL). The combined aqueous layer was back extracted with ethyl acetate (200 mL) and the combined organic layer was dried over MgSO₄. Filtration and concentration provided 10 an oil that was filtered through a silica gel column eluted with 1% methanol/methylene chloride to provide a brown solid, 1.66 g; m.p., 118-121°C.

Preparation 39

3-Benzothiazol-2-yl-phenol

3-Hydroxybenzonitrile (1 g, 8.4 mM) and 2-thioaniline (1.05 g, 8.4 mM) were 15 melted at 110°C and refluxed for about 18 hours. The black solution was poured into ice water (100 mL) causing a gray precipitate to form which dissolved in ether. The insolubles were filtered and the filtrate concentrated on a steam bath and the product precipitated by addition of petroleum ether; m.p., 144-145°C.

Preparation 40

α -Bromo-3-acetoxy acetophenone

3-Acetoxy acetophenone (22 g, 123 mM) was dissolved in carbon tetrachloride (125 mL) and treated with bromine (6.36 mL, 123 mM) dropwise over 10 minutes at room temperature. After about 4 hours the mixture was carefully poured into a 25 saturated sodium bicarbonate solution until basic. The layers were separated and the aqueous layer extracted with methylene chloride (200 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (100 mL) followed by 5% aqueous sodium bisulfite (100 mL), H₂O (100 mL) and finally saturated brine solution (100 mL). Filtration of the organic layer through a cotton plug and concentration provides an oil (31 g) of crude material used in the preparation of thiazoles.

Preparation 41

3-(2-Methylthiazol-4-yl)phenol

α -Bromo-3-acetoxy acetophenone (4.25 g, 16.5 mM) and thioacetamide (1.36 g, 18.1 mM) were refluxed in acetone (30 mL) for about 18 hours. The solvent was 35 evaporated and the crude material treated with methylene chloride which caused the product to precipitate. This was collected by filtration (2.5 g), dissolved in THF (100

-112-

mL) and treated with 3N NaOH (6 mL) which caused the phenolic product to precipitate. Filtration and rinsing with THF (20 mL) provided 1.5 g of a yellow solid; m.p., 102-103°C.

5

Preparation 42

3-(2-Substituted-thiazol-4-yl)-phenols

α -Bromo-3-acetoxy acetophenone (1 eq) and thioamide (1.1 eq) were refluxed in acetone (2-5 volumes) for about 18 hours. The solvent was evaporated and the crude material treated with methylene chloride causing product to precipitate. This was 10 collected by filtration, dissolved in THF (100mL) and treated with 3N NaOH (1.5-2 eq.). After consumption of starting material detected by (TLC) the product was extracted with ethyl acetate, washed with saturated sodium bicarbonate solution and saturated brine solution. Drying and concentration provides material suitable for preparation of glycidyl ethers.

15

Preparation 43

3-(2-Phenylthiazol-4-yl)-phenol

3-(2-Phenylthiazol-4-yl)phenol was prepared from α -bromo-3-acetoxy acetophenone and thiobenzamide as described in Preparation 42 and it was used in a crude state for the preparation of the glycidyl ether; m.p., 109-110°C.

20

Preparation 44

3-(2-Pyridin-2-yl-thiazol-4-yl)phenol

3-(2-Pyridin-2-yl-thiazol-4-yl)phenol was prepared from a α -bromo-3-acetoxy acetophenone and thiopicolinamide as described in Preparation 42 and it was used in a crude state for the preparation of the glycidyl ether; m.p., 120-121°C.

25

Preparation 45

3-(2-Pyridin-3-yl-thiazol-4-yl)-phenol

3-(2-Pyridin-3-yl-thiazol-4-yl)-phenol was prepared from a α -bromo-3-acetoxy acetophenone and thionicotinamide as described in Preparation 42; m.p. 180-181°C (CH_2Cl_2).

30

Preparation 46

3-(2-Pyridin-4-yl-thiazol-4-yl)phenol

3-(2-Pyridin-4-yl-thiazol-4-yl)phenol was prepared from α -bromo-3-acetoxy acetophenone and thioisonicotinamide as described in Preparation 42 and it was used in a crude state for the preparation of the glycidyl ether; m.p., 158-159°C.

35

-113-

Preparation 47

α -Bromo-4-hydroxyacetophenone

4-Hydroxyacetophenone (25 g) was treated with bromine (9.5 mL) dropwise over 5 15 minutes in THF (60 mL) at room temperature and stirred until the color was consumed. The whole was carefully poured into saturated sodium bicarbonate solution until basic. The aqueous layer was extracted with ether (3 x 100 mL) and the ether layer was washed with saturated sodium bicarbonate solution (100 mL) followed by 5% aqueous sodium bisulfite (100 mL), H₂O (100 mL) and finally saturated brine solution 10 (100 mL). The organic layer was dried over MgSO₄, filtered and concentrated to provide an oil (30 g) of crude material used in the preparation of thiazoles.

Preparation 48

4-(2-Substituted-thiazol-4-yl)phenol hydrobromide

α -Bromo-4-hydroxyacetophenone (1 eq) and thioamide (1.1 eq) were refluxed 15 in acetone (2-5 volumes) for about 18 hours. After cooling, the product was collected by filtration and recrystallized from methylene chloride.

Preparation 49

4-(2-Pyridin-2-yl-thiazol-4-yl)phenol hydrobromide

4-(2-Pyridin-2-yl-thiazol-4-yl)phenol hydrobromide was prepared from α -bromo-4-20 hydroxyacetophenone and thiopicolinamide as described in Preparation 48; m.p. 261-262°C.

Preparation 50

4-(2-Methylthiazol-4-yl)phenol hydrobromide

4-(2-Methylthiazol-4-yl)-phenol hydrobromide was prepared from α -bromo-4-25 hydroxyacetophenone and thioacetamide as described in Preparation 48; m.p. 250-251°C (CH₂Cl₂).

Preparation 51

4-(2-Phenylthiazol-4-yl)phenol

α -Bromo-4-hydroxyacetophenone was prepared as described above (1.68 g, 7.3 30 mM) and thiobenzamide (1.1 g, 8.0 mM) were refluxed in acetone (30 mL) for about 18 hours. After cooling, the hydrobromide salt of the product was collected by filtration and recrystallized from methylene chloride, (1.44 g, mp. 175-176°C).

-114-

Preparation 52

3-([1,3,4]-Oxadiazol-2-yl)phenol

3'-Hydroxyphenylbenzhydrazide (4.0 g, 26.3 mM) and triethylorthoformate (5.85 g, 39.5 mM) were brought to reflux in xylenes (20 mL) under N₂ for about 18 hours. (Formation of an intermediate is observed as a precipitate that redissolves upon prolonged heating). After cooling, hexanes and ethanol were added to induce precipitation of a chalky solid which was collected by filtration, 2.9 g. Recrystallization from ethanol/hexanes provided yellow granules, 1.3 g; m.p., 128-129°C.

10

Preparation 53

3-(5-Methyl-[1,3,4]-oxadiazol-2-yl)phenol

3'-Hydroxyphenylbenzhydrazide (4.0 g, 26.3 mM) and triethylorthoacetate (6.4 g, 39.5 mM) were brought to reflux in xylenes (20 mL) under N₂ for about 18 hours. (Formation of an intermediate is observed as a precipitate that redissolves upon 15 prolonged heating). Distillation of the ethanol formed in the reaction and dilution with hexanes precipitated the product which was collected by filtration, 4.23 g; m.p., 85-92°C.

Preparation 54

3-(5-Ethyl-[1,3,4]-oxadiazol-2-yl)phenol

20 3'-Hydroxyphenylbenzhydrazide (4.0 g, 26.3 mM) and triethylorthopropionate (6.96 g, 39.5 mM) were brought to reflux in xylenes (20 mL) under N₂ for about 18 hours. (Formation of an intermediate is observed as a precipitate that redissolves upon prolonged heating). Concentration and treatment with hexanes produced a yellow precipitate which was recrystallized from ethanol/hexanes, 3.0 g; m.p., 163-165°C.

25

Preparation 55

4-(5-Methyl-[1,3,4]-oxadiazol-2-yl)phenol

4'-Hydroxyphenylbenzhydrazide (5.0 g, 32.9 mM) and triethylorthoacetate (8.19 g, 50.5 mM) were brought to reflux in xylenes (30 mL) under N₂ for about 18 hours. (Formation of an intermediate is observed as a precipitate that redissolves upon 30 prolonged heating). Distillation of the ethanol formed in the reaction and dilution with hexanes precipitated light brown crystals which were collected by filtration and dried, 4.68 g; m.p., 334-335°C.

-115-

Preparation 56

4-(5-Ethyl-[1,3,4]-oxadiazol-2-yl)phenol

4'-Hydroxyphenylbenzhydrazide (5.0 g, 32.9 mM) and triethylorthopropionate (8.75 g, 49.7 mM) were brought to reflux in xylenes (30 mL) under N₂ for about 18 hours. (Formation of an intermediate is observed as a precipitate that redissolves upon prolonged heating). Distillation of the ethanol formed in the reaction and dilution with hexanes precipitated a white product which was collected by filtration and dried, 3.74 g; m.p., 204-206°C.

10

Preparation 57

3-Hydroxybenzaminoxime

3-Hydroxybenzonitrile (10.0 g, 84 mM) and hydroxylamine hydrochloride (5.84 g, 84 mM) were dissolved in ethanol (125 mL) and treated with a solution of sodium hydroxide (3.36 g, 84 mM) in H₂O (30 mL) under an atmosphere of nitrogen. This mixture was refluxed for about 5 hours and concentrated to an oil. This was treated with H₂O (300 mL), extracted with ethyl acetate (3 x 100 mL) dried over MgSO₄, filtered and concentrated to an orange oil (13.5 g) which was used without further purification.

15

Preparation 58

3-Pyridoaminoxime

20

3-Cyanopyridine (5.0 g, 48 mM) and hydroxylamine hydrochloride (3.4 g, 48 mM) were dissolved in ethanol (80 mL) and treated with a solution of sodium hydroxide (1.95 g, 48 mM) in H₂O (20 mL) under an atmosphere of nitrogen. This mixture was refluxed for about 36 hours and concentrated to an oil. This was treated with H₂O (200mL), extracted with ethyl acetate (3 x 100 mL) dried over MgSO₄, filtered and concentrated to an orange oil (5.6 g) which was used without further purification.

25

Preparation 59

3-(3'-Bromopropoxy)benzonitrile

30

3-Cyanophenol (10.0 g, 84 mM), 3-bromopropanol (20.3 mL, 114 mM), triphenylphosphine (29.7 g, 114 mM) were stirred in anhydrous THF (40 mL) at room temperature and treated with diethylazodicarboxylate (17.8 mL, 114 mM) dropwise over 5 min. under an atmosphere of nitrogen. This mixture stirred for about 5 hours then diluted with ether (500 mL) and filtered through Celite™. The filtrate was concentrated to a reddish oil which was again dissolved in ether (250 mL), diluted with hexanes (200 mL) and filtered. The filtrates were concentrated then filtered through a silica pad (300

35

-116-

g) eluting with 35% acetone/hexanes to collect the desired product as a yellow oil, 16.85 g. This material was used in its crude form.

Preparation 60

5

4-Benzhydryl-1-(3-(3-benzonitriloxy)-propyl)-piperidine

4-Benzhydrylpiperidine hydrochloride (7.8 g, 27 mM) and diisopropylethylamine (9.4 mL, 54.2 mM) were combined in dioxane (10 mL) and water (2 mL) at about 0°C causing a white slurry to form and 3-(3'-Bromopropoxy)-benzonitrile (5.0 g, 20.9 mM) in dioxane (10 mL) was added dropwise. This mixture was stirred for about 48 hours 10 at ambient temperature and then at reflux for about 2 hours. After cooling, the mixture was poured into water (200 mL) and extracted with methylene chloride (2 x 100 mL). The organic layer was washed with 1N HCl solution (2 x 250 mL), saturated aqueous sodium hydrogen carbonate solution (2 x 250 mL), filtered through a plug of cotton and concentrated to a yellow oil. Column chromatography on silica gel (200 g) eluting with 15 3% methanol/methylene chloride provided 6.95 g of an orange oil.

Preparation 61

4-Benzhydryl-1-(3-(3-benzoaminoxime)-propyl)-piperidine

4-Benzhydryl-1-(3-(3-benzonitriloxy)-propyl)-piperidine (1.0 g, 2.44 mM), hydroxylamine hydrochloride (0.18 g, 2.59 mM) and sodium hydroxide (0.22 g, 5.5 mM) 20 were combined in ethanol/water (5 mL, 4/1) and heated to reflux under an atmosphere of nitrogen for about 3 hours. The ethanol was removed in vacuo and the residue was diluted with water (100 mL) and extracted with ethyl acetate (3 x 150 mL). The organic layer was washed with brine and dried over MgSO₄, filtered and evaporated to yield 0.75 g of a white foam.

25

Preparation 62

3-(5-Substituted-[1,2,4]oxadiazol-3-yl)phenol

Amidoxime (1 eq) and an acid chloride (1 eq) were warmed to reflux in pyridine (1 volume) for about 18 hours. After cooling, the mixture was poured into H₂O and stirred for about 8 hours and the product was filtered and dried. Typically these were 30 used without further purification.

Preparation 63

3-(5-Methyl-[1,2,4]oxadiazol-3-yl)phenol

3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenol was prepared using 3-hydroxybenzamidoxime (1g, 6.6 mM) and acetyl chloride (0.52 g, 6.7 mM) in pyridine (4 mL) according to Preparation 62 to provide 0.66 g of a white powder; m.p., 87-89°C.

-117-

Preparation 64

3-(5-Pyridin-3-yl)-[1,2,4]oxadiazol-3-yl)phenol

3-(5-Pyridin-3-yl-[1,2,4]oxadiazol-3-yl)phenol was prepared using 3-
5 hydroxybenzamidoxime (1 g, 6.6 mM) and nicotinoyl chloride hydrochloride (1.2 g, 6.6
mM) in pyridine (4 mL) using Preparation 62 to provide 1.0 g of a brown precipitate;
m.p., 120-123°C.

Preparation 65

3-(5-Pyridin-4-yl)-[1,2,4]oxadiazol-3-yl)phenol

10 3-(5-Pyridin-4-yl-[1,2,4]oxadiazol-3-yl)phenol was prepared using 3-
hydroxybenzamidoxime (3 g, 19.7 mM) and isonicotinyl chloride hydrochloride (3.51 g,
19.6 mM) in pyridine (15 mL) using Preparation 62 to provide 3.65 g of a brown
precipitate; m.p., 145-146°C.

Preparation 66

15 3-(5-(3-Methoxyphenyl)-[1,2,4]oxadiazol-3-yl]pyridine

3-[5-(3-Methoxyphenyl)-[1,2,4]oxadiazol-3-yl]pyridine was prepared using 3-
pyridoamidoxime (2.2 g, 16.0 mM) and 3-methoxybenzoyl chloride (2.74 g, 16.0 mM)
in pyridine (10 mL) using Preparation 62 to provide 3.57 g white precipitate.

Preparation 67

20 3-(3-Pyridin-3-yl-[1,2,4]oxadiazol-5-yl)phenol

3-[5-(3-Methoxyphenyl)-[1,2,4]oxadiazol-3-yl]pyridine (4.0 g, 15.79 mM) and
pyridine hydrochloride (37.6 g, 325 mM) were melted together at about 160°C under
an atmosphere of nitrogen for about 30 hours. This mixture was poured into H₂O and
stirred. The precipitated product was filtered and dried, 2.9 g, mp. > 200°C.

25 Preparation 68

3-(Pyridin-2-ylamino)phenol

3-Aminophenol (3.0 g, 27.5 mM) and 2-bromopyridine (4.34 g, 27.5 mM) were
combined in acetic acid (15 mL) and heated for about 18 hours. The mixture was
concentrated in vacuo and placed on a column of silica gel (150 g). The product was
eluted with 3% methanol/methylene chloride to provide 1.2 g of an off white solid.

Preparation 69

Glycidyl ethers

35 The appropriate phenol (1 eq) and potassium t-butoxide (1.05 eq.) are combined
in anhydrous THF (2 volumes) under an atmosphere of nitrogen. After heating to reflux
for about 15 min., the mixture was cooled to ambient temperature and treated with n-

-118-

Bu₄NI (0.05 eq.) and DMF (0.05 eq.) then epibromohydrin (1.1 eq.). This mixture is brought to reflux for about 18 hours or until the reaction is deemed complete. After cooling the reaction is poured into saturated sodium hydrogen carbonate solution and the product is extracted with methylene chloride. The resulting organic layer is washed with brine then passed through a plug of cotton and concentrated to an oil. Typically this product was taken on without further purification but can be purified by column chromatography to homogeneity.

10

Preparation 70

Glycidyl ethers

The appropriate phenol (1 eq.) and sodium hydride (1.5 eq.) are combined in anhydrous DMF (3 volumes) and stirred under an atmosphere of nitrogen until hydrogen evolution ceases. Epichlorohydrin (1.2 eq.) is added and this mixture is brought to about 60°C for about 18 hours or until the reaction is deemed complete. After cooling, the reaction is poured into 50% saturated sodium chloride solution and the product is extracted with ethyl acetate (6x), dried over MgSO₄ and concentrated to an oil. Typically this product was taken on without further purification but could be purified by column chromatography to homogeneity.

15

20

Preparation 71

5-(2,3-Epoxypropoxy)-1-hydroxy-3,4-dihydroquinoline

A suspension of 1,5-dihydroxy-3,4-dihydroisoquinoline (500 mg, 3.1 mmol) and sodium hydride (129 mg 60% oil dispersion) in 15 mL of DMF was warmed to about 50°C for about 30 min.

25

Epichlorohydrin (850 mg, 3.1 mmol) was added and the resulting mixture was heated at about 90°C for about 3 hours. After it was cooled, water was added and extracted with EtOAc and CH₂Cl₂. The residue obtained after evaporation of the organic solvents was chromatographed on silica gel (1% MeOH-CH₂Cl₂) to give 295 mg of 5-(2,3-epoxypropoxy)-1-hydroxy-3,4-dihydroisoquinoline.

30

Preparation 72

5-(2,3-Epoxypropoxy)-2-hydroxy-3,4-dihydroquinoline

The title compound was prepared according to the method of Preparation 71 but using 3,4-dihydro-5-hydroxycarbostyryl instead of 1,5-dihydroxy-3,4-dihydroisoquinoline.

35

-119-

Preparation 73

5-(2,3-Epoxypropoxy)-1-tetralone

5 The title compound was prepared according to the method of Preparation 71
but using 5-hydroxytetralone instead of 1,5-dihydroxy-3,4-dihydroisoquinoline.

Preparation 74

6-(2,3-Epoxypropoxy)-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

10 The title compound was prepared according to the method of Preparation 71
but using 1,3,4,5-tetrahydro-6-hydroxy-2H-1-benzazepin-2-one instead of 1,5-dihydroxy-
3,4-dihydroisoquinoline.

Preparation 75

6-(2,3-Epoxypropoxy)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one

15 The title compound was prepared according to the method of Preparation 71
but using 2,3,4,5-tetrahydro-6-hydroxy-1H-2-benzazepin-1-one instead of 1,5-dihydroxy-
3,4-dihydroisoquinoline.

Preparation 76

6-(2,3-Epoxypropoxy)-4,5-dihydro-2-picolylamino-3H-benzazepine

20 The title compound was prepared according to the method of Preparation 71
but using 4,5-dihydro-6-hydroxy-2-picolyamine-3H-benzazepine instead of 1,5-
dihydroxy-3,4-dihydroisoquinoline.

Preparation 77

4,5-Dihydro-6-hydroxy-2-picolyamine-3H-benzazepine

25 A suspension of 1,3,4,5-tetrahydro-6-hydroxy-2H-1-benzazepin-2-one (500 mg,
2.82 mmol) in 2.5 mL each of pyridine and acetic acid was stirred at room temperature.
Excess reagents were removed under reduced pressure and the residue was triturated
with CH_2Cl_2 to give 540 mg (87%) of 1,3,4,5-tetrahydro-6-acetoxy-2H-1-benzazepin-2-
one; MS 219.

30 A suspension of 1,3,4,5-tetrahydro-6-acetoxy-2H-1-benzazepin-2-one (50 mg,
0.23 mmol) and Lawesson reagent (65 mg, 0.16 mmol) in 3 mL of toluene was refluxed
for about 1 h. The residue obtained after evaporation of the solvent was
chromatographed on silica gel PTLC (5% $\text{MeOH}-\text{CH}_2\text{Cl}_2$) to give 51 mg (94%) of 1,3,4,5-
tetrahydro-6-acetoxy-2H-1-benzazepin-2-thione; MS 235.

35 To a solution of 1,3,4,5-tetrahydro-6-acetoxy-2H-1-benzazepin-2-thione (235 mg,
1.0 mmol) in 25 mL of CH_2Cl_2 was added at 0° 295 mg (2.0 mmol) of trimethyloxonium
tetrafluoroborate. After stirring at room temperature for about 30 min. water was added

-120-

and the CH_2Cl_2 layer was separated. Drying over Na_2SO_4 and removal of the solvent gave 229 mg of 4,5-dihydro-6-acetoxy-2-methylthio-3H-benzazepine.

A mixture of 4,5-hydro-6-acetoxy-2-methylthio-3H-benzazepine (240 mg, 0.96 mmol) and 2-picolyamine (209 mg, 1.92 mmol) in 4 mL of 2-(2-ethoxyethoxy) ethanol was heated at about 150°C for about 3 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel ($\text{CH}_2\text{Cl}_2 \rightarrow 20\% \text{ MeOH-CH}_2\text{Cl}_2$) to give 207 mg (81%) of 4,5-dihydro-6-hydroxy-2-picolylamino-3H-benzazepine: MS 267.

10 Preparation 78

N-Hydroxybenzhydrylpiperidine

Benzhydrylpiperidine (1 eq., 1.818 g, 7.63 mmol), Na_2HPO_4 (5 eq., 5.4 g, 38.0 mmol) and 1:1 $\text{Et}_2\text{O/THF}$ (40 ml) were combined with dibenzoyl peroxide (1.1 eq., 2.040 g, 8.42 mmol) while THF was introduced via an addition funnel and the reaction mixture was stirred under N_2 at about 20°C. At the end of the addition, the white suspension was heated at reflux overnight. After 18 hours the solution was cooled; a white precipitate formed during the cooling process. The white precipitate was filtered and washed with CH_2Cl_2 . The filtrate was concentrated in vacuo and resuspended in CH_2Cl_2 . The resulting yellow solution was washed sequentially with 10% aqueous Na_2CO_3 (2 x 15 ml) and brine. The organic layers were dried over $\text{MgSO}_4(\text{s})$ filtered and concentrated in vacuo to give 2.75 g of a sticky yellow solid. Flash chromatography on silica using 15% EtOAc/hexanes gave 1.72 g of a white/yellow powder, LSIMS, 372 MH^+ .

The white/yellow powder was dissolved in about 30 ml of Et_2O and added dropwise to 0.203 g (5.19 mmol) of potassium metal in 10 ml of MeOH and stirred at room temperature for about 22 hours. The resulting cloudy yellow solution was concentrated in vacuo, resuspended in H_2O and extracted with Et_2O . The organic layers were combined, dried over $\text{MgSO}_4(\text{s})$ filtered and concentrated in vacuo to give 1.20 g of a yellow solid. Chromatography on silica using 100% EtOAc gave 0.89 g of an off-white solid, LSIMS, 268 MH^+ .

25 Preparation 79

2-Ethyl-benzothiazol-7-ol

A solution of 3-methoxyphenyl isothiocyanate (5.00 g, 30.3 mmoles) in dry THF (15 mL) was added dropwise over 10 min. with stirring at about -10°C to ethyl-magnesium bromide (60.6 mmoles) in THF (30 mL). After 90 min. the reaction was

-121-

5 quenched with saturated aqueous NH₄Cl (25 mL) and extracted with EtOAc (3 x 50 mL). Organic extracts were pooled, washed with brine, dried over MgSO₄(s), filtered and concentrated in vacuo to afford the crude propionyl thioamide as a greenish-yellow oil (5.92 g; GC-MS m/z 195). This thioamide was cyclized without further purification using the alkaline K₃Fe(CN)₆ procedure as described in Preparation 1. The organic extracts from this reaction was flash chromatographed on silica using 10→15% EtOAc/hexanes to separate pure 7-methoxy-2-ethyl-benzothiazole (1.13 g), from its later eluting 5-methoxy isomer (1.53 g). The 7-methoxy derivative was deprotected using the 10 pyridinium hydrochloride melt as described in Preparation 1 to produce 2-ethyl-benzotriazol-7-ol (0.790 g; GC-MS m/z 179).

Preparation 80

2-Isopropyl-benzothiazol-7-ol

15 The crude yellow solid thioamide (5.40 g) obtained from the reaction of isopropylmagnesium chloride (56 mmoles) with 3-methoxyphenyl isothiocyanate (4.64 g, 28.1 mmol) in a manner analogous to that described in Preparation 79, was cyclized using the alkaline K₃Fe(CN)₆ methodology outlined in Preparation 1. The residue from the organic extracts was chromatographed on silica (10% EtOAc/hexanes) to resolve the faster eluting 7-methoxy-2-isopropyl-benzothiazole (2.27 g; GC-MS m/z 207) from its 5-methoxy isomer (1.1 g; GC-MS m/z 207). Deprotection using pyridinium 20 hydrochloride for about 24 h at about 160° (see Preparation 1) afforded 2.00 g of crude product which was flash chromatographed (20% acetone/hexanes) to yield pure 2-isopropyl-benzothiazol-7-ol (1.18g; LC-MS m/z 194 (MH⁺)).

25 Preparation 81

2-Butyl-benzothiazol-7-ol

30 This material was prepared by cyclization of the thioamide generated from 3-methoxyphenyl isothiocyanate (5.02 g; 30.4 mmol) and n-butyllithium (63 mmol), and subsequent deprotection of the resolved 7-methoxy derivative as described in Preparation 79.

Preparation 82

2-(2-Hydroxy-2-methyl)propyl-benzothiazol-7-ol

35 The 7-methoxy-2-methylbenzothiazole (720 mg, 4.0 mmol) produced in Preparation 1 was dissolved in dry THF (15 mL) and chilled to about -78°C. Phenyllithium (2.45 mL of 1.8 M in cyclohexane/Et₂O) was added dropwise over about 5 min. After stirring for about 10 min. at about -78°C, acetone (1.3 eq, 5.2 mmol, 385

-122-

μ L) was added dropwise and stirring continued for about 10 min. at about -78°C and about 1 h. at about 0°C before quenching with 2M NH₄OAc (15 mL). EtOAc (15 mL) was added and the separated organic phase was washed with brine, dried over 5 Na₂SO₄(s), filtered and concentrated in vacuo. The residue was flash chromatographed on silica (20→25% EtOAc/hexanes) to afford first recovered starting material (375 mg) followed by the desired 7-methoxy-2-[(2-hydroxy-2-methyl)propyl]-benzothiazole (430 mg). This material (388 mg) was dissolved in dry CH₂Cl₂ (5 mL), chilled to about -78°C and treated with BBr₃(299 μ L). The resulting solution was allowed to warm to about 10 20°C, and after about 5 h at about 20°C was added dropwise with stirring to NaHCO₃ (1.33 g) in H₂O (25 mL) at about 5-10°C. The pH of the aqueous phase was adjusted to ~ 7 and extracted with CH₂Cl₂. The residue (360 mg) from the organic extracts containing 2-bromo and 2-hydroxy 2-adducts was hydrolyzed with silver(I) 15 trifluoroacetate (1.1 g) in DMF (15 mL)/H₂O(80 mL) at about 20°C for about 16 h. The mixture was treated with saturated Na₂CO₃ (20 mL) at about 60°C for about 30 min., cooled to about 20°C, filtered through celite to remove precipitated Ag₂CO₃(s), pH adjusted to 6-7, and extracted with 15% i-PrOH/Et₂O (3 x 20 mL). Pooled organic extracts were washed with brine, dried over Na₂SO₄(s) and concentrated in vacuo to 20 afford 219 mg of crude (\geq 75% pure by RP-HPLC) 2-(2-Hydroxy-2-methyl)propyl-benzothiazol-7-ol (LC-MS m/z 224 (MH⁺)) which was used without further purification.

Preparation 83

2-(Pyridin-4-yl)benzothiazol-7-ol

This material (LC-MS m/z 229 (MH⁺)) was prepared from m-anisidine (13.71 g, 25 111.3 mmoles) and isonicotinoyl chloride hydrochloride (19.82 g, 111.3 mmol) utilizing the procedure as described for Preparation 33 for the acylation, conversion to the thioamide, K₃Fe(CN)₆ mediated cyclization and deprotection.

Preparation 84

2-(Morpholin-4-yl)benzothiazol-7-ol

Morpholine (7.93 g, 91.0 mmol) was added to 3-methoxyphenyl isothiocyanate 30 (5.01 g, 30.3 mmol) in t-BuOH (15 mL) and the stirred mixture was heated to about 70°C for about 3 h. Most of the solvent was removed in vacuo at about 35°C and the concentrate was partitioned between CHCl₃ (100 mL) and 0.5 M aqueous HCl (100 mL). The organic phase was washed with 0.5 M HCl (2 x 50 mL) and brine, dried over 35 MgSO₄(s), filtered and concentrated in vacuo to afford the crude thiourea as a light yellow powder (7.64 g; LC-MS m/z 253 (MH⁺)). This material was cyclized using

-123-

5 $K_3Fe(CN)_6$ according to the procedure outlined in Preparation 32. The residue from the resulting organic extracts was purified by flash chromatography on silica (20-30% EtOAc/hexanes) to afford 2.92 g of pure 7-methoxy-2-(morpholin-4-yl)benzothiazole (GC-MS m/z 250) and 0.915 g of the 5-methoxy isomer. Deprotection of the 7-methoxy derivative (2.92 g, 11.7 mmol) with molten pyridinium hydrochloride at about 160°C as in Preparation 32 yielded 2-(morpholin-4-yl)benzothiazol-7-ol (1.85 g; LC-MS m/z 237 (MH⁺)).

10 Preparation 85

2-(4-Methyl-piperazin-1-yl)benzothiazol-7-ol

15 This material was prepared by the cyclization and deprotection of the thiourea obtained from the reaction of 3-methoxyphenyl isothiocyanate (5.01 g, 30.3 mmol) with N-methyl piperazine (15.16 g, 151.4 mmol) in refluxing t-BuOH in a manner analogous to that of Preparation 84. (LC-MS m/z 250 (MH⁺)).

15 Preparation 86

2-(4-Trifluoroacetyl-piperazin-1-yl)benzothiazol-7-ol

20 The thiourea obtained from the reaction of 3-methoxyphenyl isothiocyanate (5.02 g, 30.4 mmol) with piperazine (13.01 g, 151 mmol) in refluxing t-BuOH was cyclized with $K_3Fe(CN)_6$ and subsequently deprotected with molten pyridinium hydrochloride at about 160°C according to the procedure described for Preparation 84, but without the chromatographic separation of the 5- and 7- isomers. The resulting 2-(piperazinyl)-benzothiazol-5-ol and -7-ol mixture (2.35 g, 10 mmol) was dissolved in trifluoroacetic acid (20 mL) and chilled to about 0-5°C. Trifluoroacetic anhydride (3.4 mL, 24 mmol) was added dropwise over several minutes. After stirring for about 3 h. at about 20°C the mixture was concentrated in vacuo at about 35°C and then redissolved in H₂O (50 ml) with adjustment of the pH to 6-7 by careful addition of saturated aqueous K₂CO₃. The mixture was stirred for about 30 min. at about 20°C, diluted with H₂O (60 mL) and extracted with 5% MeOH in CH₂Cl₂ (1 x 100 mL, 2 x 40 mL). Pooled organic extracts were dried over Na₂SO₄(s) and concentrated in vacuo to afford a mixture of the 2-(4-trifluoroacetyl)piperazin-1-yl) benzothiazol-5-ol and -7-ol isomers as a foamy solid (2.12 g; GC-MS m/z 331). The isomers were resolved by flash chromatography on silica (35% EtOAc/hexanes) to yield 820 mg of the pure 2-(4-trifluoroacetyl-piperazin-1-yl)benzothiazol-7-ol as the faster eluting isomer.

-124-

Preparation 87

1-(4-Fluoro-3-methyl-phenyl)cyclohexylamine

5 Cyclohexanone (5.0 mL, 47.5 mmol) was added dropwise at about 0°C to 4-fluoro-3-methylphenyl magnesium bromide (50 mmol) in THF (50 mL). The mixture was allowed to warm to about 20°C and stirred for about 1 h. The mixture was carefully added to 5% AcOH in H₂O (100 mL) at about 5°C and extracted with Et₂O (150 mL). Organic extracts were dried over Na₂SO₄(s), filtered and concentrated in vacuo to a colorless syrup of crude 1-(4-fluoro-3-methyl)cyclohexanol (9.78 g, GC-MS m/z 208).

10 The alcohol from above (9.6 g) was dissolved in CHCl₃ (100 mL) and NaN₃(s) (10 g, 155 mmol) was added. The stirred mixture was cooled to about 0-5°C and TFA (30 g) was added dropwise over about 5 min. After stirring for about 16 h. at about 20°C, H₂O (150 mL) and CHCl₃ (150 mL) were added to the thick slurry. The organic phase obtained after about 10 minutes of stirring was washed with H₂O (2 x 100 mL) and aqueous 5% NaHCO₃ (2 x 50 mL), dried over Na₂SO₄(s) and concentrated in vacuo to obtain the crude 1-(4-fluoro-3-methylphenyl)cyclohexyl azide (9.25 g, GC-MS m/z 233) which was reduced without further purification.

20 The crude azide (9.2 g, ≤ 44 mmol) was dissolved in MeOH (100 mL) at about 0-5°C and Mg(s) (1.8 g of 40-80 mesh) was added in 3 portions over about 10 min. At about 1½ h. intervals additional Mg(s) (2 x 1.8 g) was added. The mixture was allowed to stir for about 16 h. at about 20°C and then 2N NH₄OH (200 mL) and Et₂O (500 mL) were added. The mixture was filtered and the cake was washed with Et₂O. Pooled organic phases were washed with aqueous 5% NaHCO₃, dried over MgSO₄(s), filtered and concentrated in vacuo to afford 7.5 g crude amine as an oil. This residue was dissolved in dry Et₂O (80 mL) and treated dropwise with 1M HCl in Et₂O (35 mL) at about 5°C while stirring. After 15 min. at about 5°C the precipitated hydrochloride salt of 1-(4-fluoro-3-methylphenyl)cyclohexyl-1-amine was filtered, washed with Et₂O and pet. ether and dried in vacuo (3.92 g; LC-MS m/z 208 (MH⁺)).

30 Preparation 88

1-Phenylcyclohexylamine

35 1-Phenylcyclopentanol (16.3g, 100 mmol) was treated with NaN₃(s) (20 g, 310 mmol) and TFA (65 g) in CHCl₃ (170 mL) at about 0-5°C, according to the procedure described in Preparation 87, to produce crude 1-phenyl-cyclohexylazide (18.6 g, GC-MS m/z 187).

-125-

The crude azide (18.0 g, \leq 96 mmol) was dissolved in dioxane (300 mL) with triphenylphosphine (40 g, 152 mmol) and the stirred solution was refluxed for 4 h. under N₂ (g) before adding H₂O (9 mL, 0.5 mol). After about 46 h. further reflux, solvent was removed in vacuo at about 45-50°C and residual moisture was removed by azeotropic distillations in vacuo with CH₃CN and Et₂O, respectively. The syrupy residue was dissolved in boiling Et₂O and chilled to about 0°C for about 16 h. Precipitated Ph₃PO was removed by filtration, and 1M HCl in Et₂O (90 mL) was added dropwise at about 5°C to the etherol filtrate to precipitate the desired 1-phenyl-cyclohexylamine as its HCl salt (12.7g, LC-MS m/z 162 (MH⁺)) which was recrystallized from CHCl₃/i-Pr₂O before use.

Preparation 89

1-(4-*tert*-Butyl-phenyl)cyclohexylamine

4-*tert*-Butylphenylmagnesium bromide (100 mmol in 50 mL Et₂O) and cyclopentanone (8.0 mL, 90 mmol) were reacted in a manner analogous to that described in Preparation 87 to produce the intermediate alcohol and subsequently the azide. Crude azide (10.5g, \leq 43 mmol) was reduced with Ph₃P/H₂O in dioxane as described in Preparation 88 to afford the desired 1-(4-*tert*-butylphenyl)cyclohexylamine which was isolated from Et₂O by precipitation as its HCl salt (2.8g; GC-MS m/z 217).

Preparation 90

2-Phenyl-decahydronaphthalen-2-ylamine

This material was prepared from *cis/trans*-2-tetralone and phenylmagnesium bromide utilizing a procedure analogous to those described in Preparation 89. The crude HCl salt of the amine was purified by preparative C18-RP-HPLC using a 15% \rightarrow 100% CH₃CN pH 4.5, 50 mm NH₄OAc gradient, followed by concentration in vacuo and extraction of the free-base into Et₂OAc from 1N NaOH to obtain a 2:1 mixture of pure *trans/cis*-2-phenyl-decahydronaphthalen-2-ylamine.

Preparation 91

5-*tert*-Butyl-3-phenyl-bicyclo[2.2.1]hept-5-en-2-ylamine

2-Cyclopenten-1-one (14.2 mL, 0.17 mol) was added dropwise over about 30 min. at about -78°C to t-BuLi (340 mmol) in dry THF (450 mL). The reaction was allowed to warm to about 20°C and then chilled to about -78°C to quench with NH₄Cl (18.2 g). Solvent was removed in vacuo and the residue was partitioned between Et₂O (300 mL) and brine (100 mL). The organic phase was washed with brine, dried over MgSO₄(s), filtered and concentrated in vacuo. The residue of crude 1-*tert*-

-126-

5 butylcyclopent-2-en-1-ol (23.8 g) was treated with benzenesulfonic acid (0.24 g) in refluxing Et₂O for 1.5 h. Solvent was removed in vacuo and the residue was vacuum distilled (12 mm, ~27-30°C) to obtain pure 2-*tert*-butylcyclopentadiene (4.2 g). This
10 diene (1.3 g, 10.7 mmol) was dissolved in xylene (5 mL) along with a crystal of hydroquinone and *trans*- β -nitrostyrene (1.95g, 13.1 mmol). The tube was sealed under N₂(g) and heated to about 140°C for about 10 h. Flash chromatography on silica (30% CH₂Cl₂/hexanes) afforded 1.79 g (GC-MS m/z 271) of the nitro derivative which was reduced by dropwise addition of an ethereal (10 mL) solution over 20 min. to LiAlH₄ (0.5 g) in Et₂O (25 mL). The mixture was refluxed for about 5 h. and quenched by serial
15 additions of H₂O (0.5 mL), 15% NaOH (0.5 mL) and H₂O (1.5 mL), respectively. The mixture was filtered and the filtrate was washed with saturated aqueous NaHCO₃ and brine, dried over MgSO₄(s), filtered, and concentrated in vacuo. The residue (1.1 g) was dissolved in dry Et₂O (6 mL), chilled to about 5°C, and treated dropwise with 1M
HCl in Et₂O (6 mL) to precipitate the desired amine as its HCl salt (610 mg; LC-MS m/z 242).

Preparation 92

3-(2,6-Dichlorophenyl)bicyclo[2.2.1]hept-5-en-2-ylamine

20 Cyclopentadiene (2.39 g, 36.2 mmol) and 2,6-dichloro-*omega*-nitrostyrene (3.3 g, 15.1 mmol) in xylene (4 mL) with a crystal of hydroquinone under N₂(g) were heated in a sealed tube at about 120°C for about 40 h. Flash chromatography on silica in 5% EtOAc/hexanes yielded 2.94 g of a mixture of the desired nitro intermediate and the nitro derivative resulting from a second Diels-Alder addition of cyclopentadiene to the initial desired product (LC-MS m/z 303 (M+NH₄⁺) and 367 (M+NH₄⁺), respectively). The 2.0 g of this mixture in Et₂O (110 mL)/MeOH (14 mL)/H₂O (6 mL) was treated with an excess of aluminum-amalgam at about 20°C for about 6 h. The mixture was filtered through celite, and the filtrate was concentrated in vacuo. The residue was purified by preparative C18-RP-HPLC using a gradient from 5% to 100% CH₃CN/pH 4.5, 50 mM NH₄OAc, to yield the desired amine which was recovered as its free-base (370 mg; LC-MS m/z 254 (MH⁺)) following concentration in vacuo and extraction into EtOAc from 1 M NaOH.

-127-

Preparation 93

3-(2-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-ylamine

5 This material (LC-MS m/z 220 (MH⁺)) was prepared via the nitro derivative according to the procedure described in Preparation 92 but starting instead with 2-chloro-omega-nitrostyrene and cyclopentadiene.

Preparation 94

trans-2-Phenylcyclopent-1-ylamine

10 A mixture of 1-phenylcyclopentene (5.77g, 40.0 mmol) and Et₃SiH (40 mmol, 4.65g, 6.40 mL) was added dropwise over about 10 min. at about -78°C to 1.0 M BCl₃ in CH₂Cl₂ (40 mL, 40 mmol). The resulting solution was allowed to warm to about 20°C and stirred for about 2.5 h. before the removal of the solvent in vacuo. The residue was dissolved in 1,2-dichloroethane (60 mL) and heated to about 60°C before 15 azidotrimethylsilane (4.83g, 5.57 mL, 42 mmol) was added dropwise. MeOH (15 mL) was added and the mixture was refluxed for about 16 h. under N₂ (g).

15 H₂O (60 mL) was added followed by conc. HCl (30 mL). The organic phase was separated and washed further with 3N HCl (2 x 30 mL). Pooled aqueous extracts were washed with Et₂O (1 x 20 mL), and then the pH was adjusted to 13-14 with 6N NaOH. 20 The crude free-base of the desired amine was extracted into Et₂O (80 mL) and this ether extract was dried over MgSO₄(s), filtered and concentrated in vacuo to afford 1.1g of a syrup. This residue was dissolved in Et₂O (20 mL) and treated with 1M HCl in Et₂O (8 mL, 8 mmol) at about 5°C. 2-Phenyl-cyclohex-1-ylamine (335g; LC-MS m/z 162 (MH⁺)) was obtained as its pure HCl salt by filtration of the resulting precipitate, which 25 was then washed with Et₂O and recrystallized from CHCl₃/i-Pr₂O.

Preparation 95

2-Methyl-7-[2-(2-methyl-oxiranyl)-ethoxy]-benzothiazole

2-Methyl-7-hydroxybenzothiazole was alkylated with 3-methyl-3-buten-1-ol according to Method VI. The product of this alkylation (0.30 g, 1.28 mmol) was 30 dissolved in CH₂Cl₂ at about 0°C to which was then added a solution of m-chloroperbenzoic acid (0.95 g, 5.53 mmol) in CH₂Cl₂. The reaction was allowed to warm to room temperature and after about 0.5 h the reaction was complete. 1N NaOH was added, the layers separated and the organic layer was washed with additional 1N NaOH and H₂O. The organic layer was then dried over MgSO₄ and the solvent was removed by 35 rotary evaporation to give the title compound (0.20 g, 63%) as a yellow oil which was used in subsequent reactions without further purification.

-128-

Preparation 96

3-Amino-1-benzhydrylazetidine

5 3-Mesyloxy-1-benzhydrylazetidine (30.32 g, 95.5 mmol), potassium phthalimide (21.59 g, 116.53 mmol) and hexadecyl tributylphosphonium bromide (5.92 g, 11.7 mmol) were added to toluene (600 mL) and the mixture stirred at room temperature overnight. The reaction was then heated at reflux for 3 h. The solid was removed by filtration, washed with EtOAc and the combined organics then washed with H₂O. After 10 drying over Na₂SO₄, the organics were treated with charcoal and then concentrated to an oil. Addition of isopropyl ether induced crystallization of the product (16.37 g, 46%).

15 The phthalimide protecting group was removed by treatment with hydrazine in methanol at reflux for 4 h. The solids were removed by filtration and the filtrate concentrated to give the title compound as a yellow oil (94%). This material was used without further purification.

Preparation 97

6-Allyl-2-methyl-7-(oxiran-2-ylmethoxy)

20 To 7-hydroxy-2-methylbenzothiazole (500 mg, 3.0 mmol) in DMF (3 mL) was added K₂CO₃ (459 mg, 3.32 mmol) followed by allyl bromide (287 uL, 3.32 mmol). The reaction was heated at about 50° C for about 4 hours and then poured into water. The aqueous mixture was extracted with EtOAc, the combined organic layers were dried over Na₂SO₄, and the solvent then removed by rotary evaporation. The resulting oil crystallized on standing to give 7-allyloxy-2-methyl-benzothiazole as yellow crystals (440 mg, 71%); LSIMS m/z 206, m.p. 38-39° C.

25 In a small sublimation apparatus, 7-allyloxy-2-methylbenzothiazole (242 mg, 1.18 mmol) was heated at about 200° C for about 5 minutes. Crystals were scraped from the cold fingers to give 6-allyl-7-hydroxy-2-methylbenzothiazole (150 mg, 62%) which was used in the next step without further purification.

30 The corresponding glycidyl ether was prepared from 6-allyl-7-hydroxy-2-methylbenzothiazole using Method I (94% yield).

Preparation 98

4-Chloro-7-hydroxy-2-methylbenzothiazole

35 6-Chloro-m-anisidine (5 g, 26 mmol) was dissolved in CH₂Cl₂ to which was added triethylamine (3.6 mL, 26.4 mmol) and finally acetyl chloride (1.9 mL, 26.4 mmol) dropwise. The reaction was stirred at room temperature for several hours and then poured into water. The layers were separated and the organic dried over sodium

-129-

sulfate. Solvent was removed by rotary evaporation to give 3-acetamide-4-chloroanisole (4.49 g, 95%) as a purple oil which was used without purification.

5 To the material above (4.4 g, 22 mmol) in toluene was added Lawesson's Reagent (18 g, 44 mmol) and the reaction heated at reflux for about 2 hours. After cooling to about 40° C, aqueous sodium carbonate was added and the mixture stirred with ether and the layers were separated. The aqueous layer was extracted with more ether and the combined organic layers were dried over sodium sulfate. The solvent was removed by rotary evaporation and the residue purified by column chromatography 10 (silica gel, 9/2/0.5 CH₂Cl₂/ hexanes/ methanol) to give 4-chloro-3-thioacetamidoanisole (2.0 g, 42%) m.p. 92-93° C; mass spec. m/z 216.

The above material was cyclized to 4-chloro-7-methoxy-2-methylbenzothiazole by the method described in Preparation 1.

15 The title compound was prepared from 4-chloro-7-methoxy-2-methylbenzothiazole by cleavage of the methyl ether with pyridine hydrochloride as described in Preparation 1, m.p. 225° C (decomposition), mass spec. m/z 200.

20

25

30

35

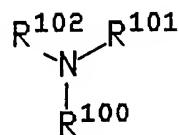
-130-

Claims

What is claimed is:

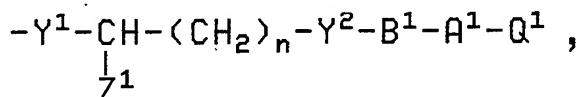
1. A compound of the formula

5

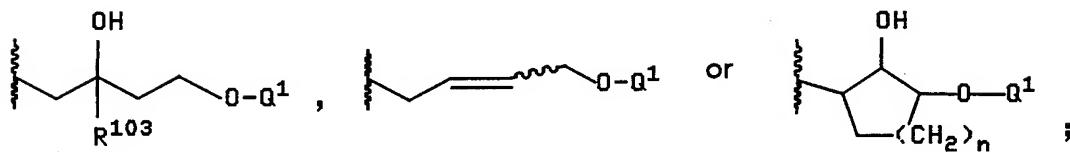


(I)

10

and the pharmaceutically acceptable acid addition salts thereof wherein R^{100} is

15

20 where R^{103} is $-(\text{C}_1-\text{C}_4)\text{alkyl}$; Y^1 is selected from the group consisting of oxygen, methylene, ethylene and a covalent bond; Z^1 is selected from the group consisting of H, OH, CF_3 , NO_2 , and $-\text{O}(\text{C}_1-\text{C}_4)\text{alkyl}$;25 n is 1 or 2; Y^2 is selected from the group consisting of O, S, NH, NCH_3 , a covalent bond,30 B^1 is selected from the group consisting of a covalent bond and optionally substituted phenyl,

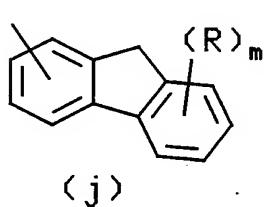
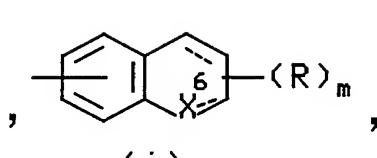
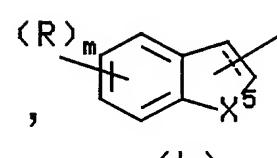
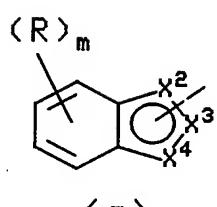
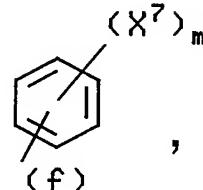
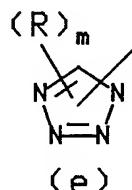
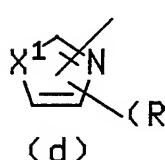
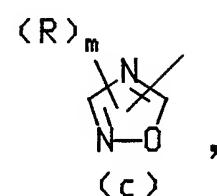
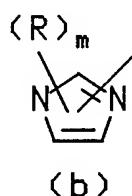
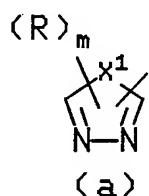
where the optionally substituted phenyl is optionally substituted with one or two substituents independently selected from the group consisting of $(\text{C}_1-\text{C}_4)\text{alkyl}$, halo, $(\text{C}_1-\text{C}_4)\text{alkoxy}$, amino, N-alkylamino having 1 to 4 carbons, N,N-dialkylamino having a total of 2 to 4 carbons, nitrile and nitro;

35

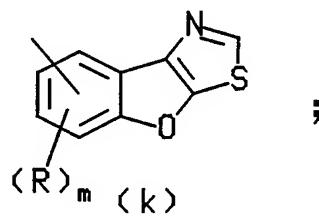
-131-

5 A¹ is selected from the group consisting of a covalent bond, (C₁-C₄)alkylene, O, S and NH;

10 Q¹ is selected from the group consisting of



65 and



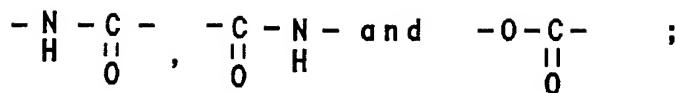
75 wherein _____ represents a single or a double bond;

80 X¹ is O or S;

85 X², X³ and X⁴ are each independently selected from the group consisting of C, N, CH, NH, O and S, provided that no more than one of X², X³ and X⁴ is O or S;

90 X⁵ is selected from the group consisting of

-132-



5

X^6 is selected from the group consisting of C, CH, N, NH,



10

X^7 is selected from the group consisting of (C_1 - C_4)alkyl, halo, (C_1 - C_4)alkoxy, amino, nitrile, nitro, N-alkylamino having 1 to 4 carbons and N,N-dialkylamino having a total of 2 to 6 carbons;

15

m is 1, 2 or 3;
and each R is independently selected from the group consisting of hydrogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, halo, N-alkylamino having 1 to 4 carbons, N,N-dialkylamino having a total of 2 to 6 carbons, amino, nitro, nitrile, hydroxyl, alkylthio having 1 to 3 carbons, =N-OCH₃, =N-OH, pyridinyl, (pyridin-1-yl)methylene, piperazinyl, 4-alkylpiperazinyl having 1 to 4 carbons in the alkyl portion, morpholino, -CH₂-C(OH)(CH₃)₂, allyl, -NHCOCH₃, aralkylamino having 1 to 4 carbons in the alkyl portion and optionally substituted phenyl,

20

where the optionally substituted phenyl is optionally substituted with 1 or 2 substituents independently selected from the group consisting of (C_1 - C_4)alkyl, halo, (C_1 - C_4)alkoxy, amino, nitrile, nitro, N-alkylamino having 1 to 4 carbons and N,N-dialkylamino having a total of 2 to 6 carbons;

25

R^{101} is the same as R^{100} or is selected from the group consisting of hydrogen, (C_1 - C_4)alkyl, alkenylphenyl having 2 to 4 carbons in the alkenyl portion, and alkylphenyl having 1 to 4 carbons in the alkyl portion and the phenyl portion is optionally substituted with one or two substituents independently selected from the group consisting of (C_1 - C_4)alkyl, halo, (C_1 - C_4)alkoxy, amino, nitrile, nitro, N-alkylamino having 1 to 4 carbons and N,N-dialkylamino having a total of 2 to 6 carbons;

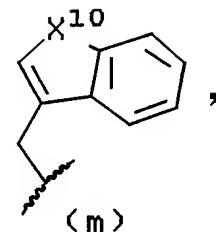
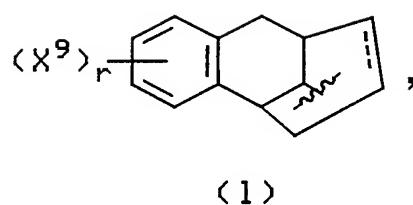
30

R^{102} is selected from the group consisting of hydrogen,

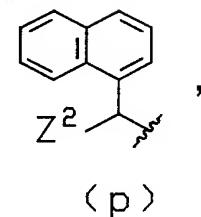
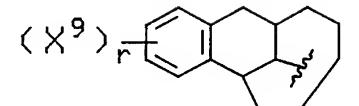
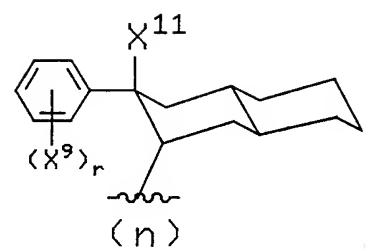
35

-133-

5

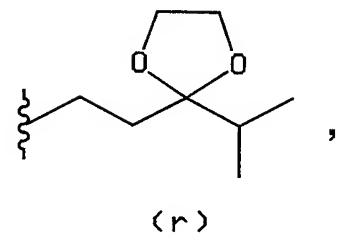
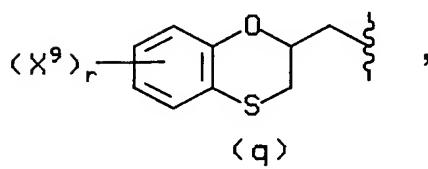


10

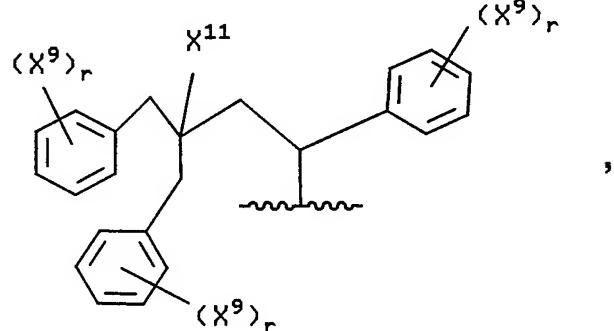
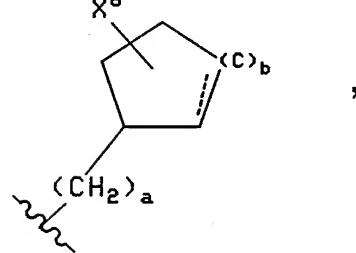


15

20



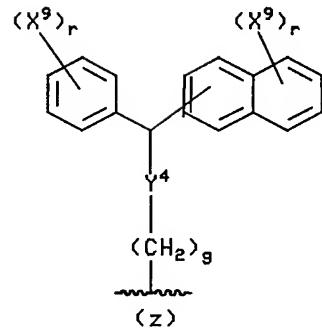
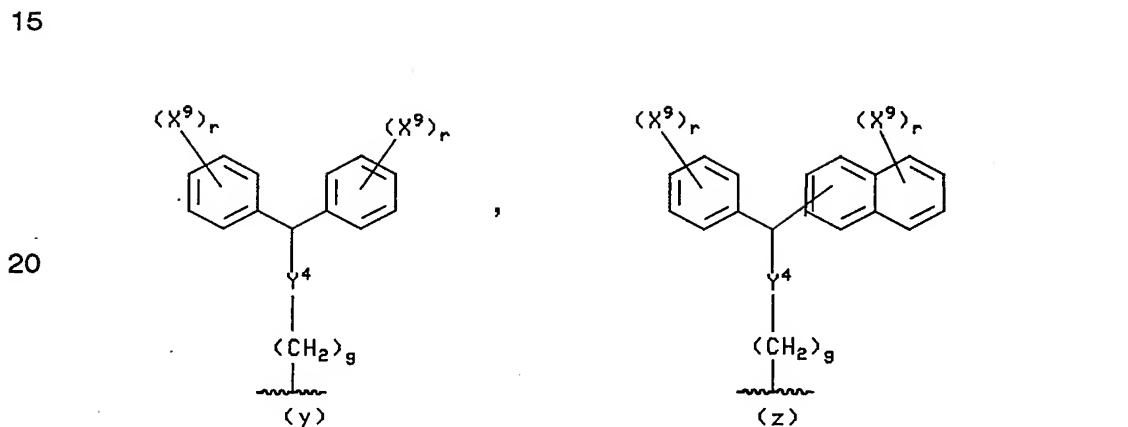
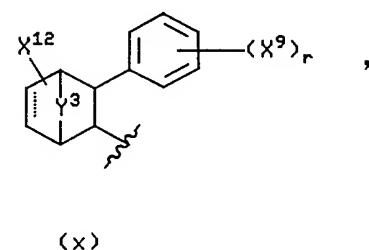
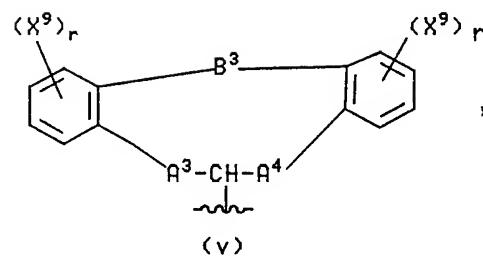
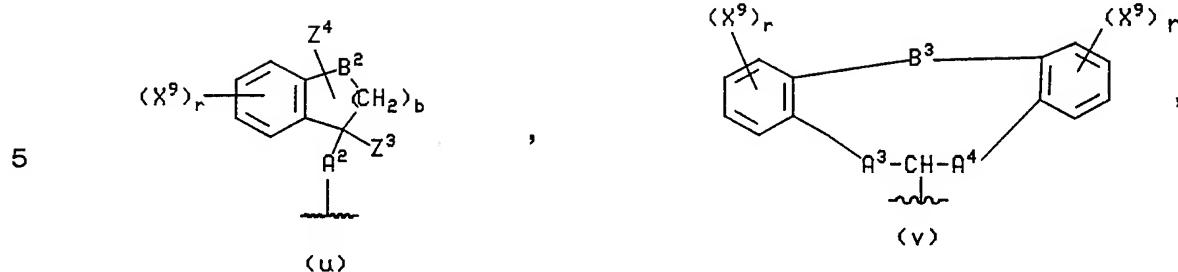
25



30

35

-134-



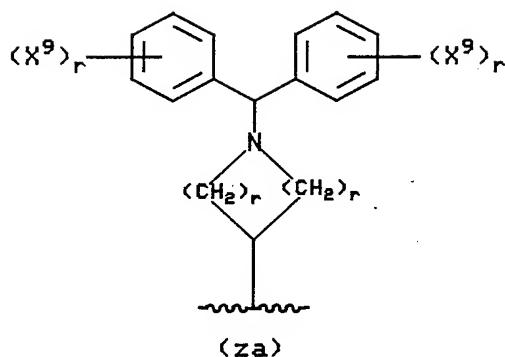
25

30

35

-135-

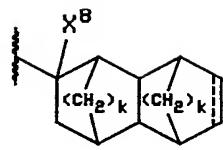
5



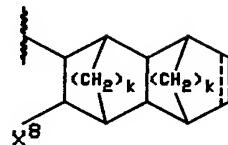
10

(za)

15



and



(zb)

(zc)

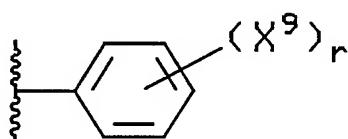
20

where r for each occurrence is independently 1 or 2;

a is 0, 1, 2 or 3;

X8 is selected from the group consisting of (C1-C4)alkyl and

25



where r is as defined above;

30

X9 for each occurrence is independently selected from the group consisting of hydrogen, hydroxy, chloro, fluoro, (C1-C4)alkoxy, CF3 and (C1-C4)alkyl;

X10 is S or O;

X11 is hydrogen or hydroxy;

Z2 is hydrogen or methyl;

35

b is 0, 1, 2 or 3;

-136-

A² is selected from the group consisting of a covalent bond, CHCH₃ and (C₁-C₄)alkylene;

B² is selected from the group consisting of CH₂, CH and S;

5 Z³ is selected from the group consisting of hydrogen, phenyl and hydroxy;

Z⁴ is selected from the group consisting of hydrogen, phenyl and (C₁-C₄)alkyl;

B³ is selected from the group consisting of S, O, -CH₂O-, -CH₂S-, -CH₂-,
-CH₂-CH₂-, -CH=CH- and no bond;

A³ and A⁴ are independently a covalent bond or methylene;

10 X¹² is selected from the group consisting of hydrogen, (C₁-C₄)alkyl, phenyl and benzyl;

Y³ is selected from the group consisting of (C₁-C₄)alkylene, O, S, -CH₂O- and -CH₂S-;

Y⁴ is selected from the group consisting of S, O, NH and a covalent bond;

15 g is an integer from 1 to 4;

k for each occurrence is independently 0, 1 or 2; and

— represents a single or a double bond;

or R¹⁰¹ and R¹⁰² are taken together with the nitrogen to which they are attached and form heterocycles selected from the group consisting of

20

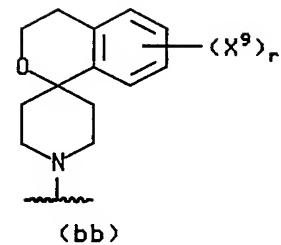
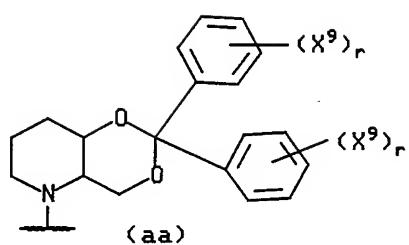
25

30

35

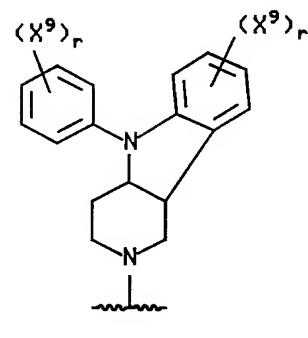
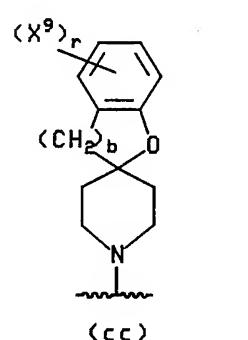
-137-

5



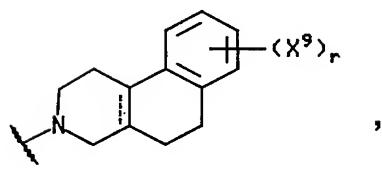
10

15



20

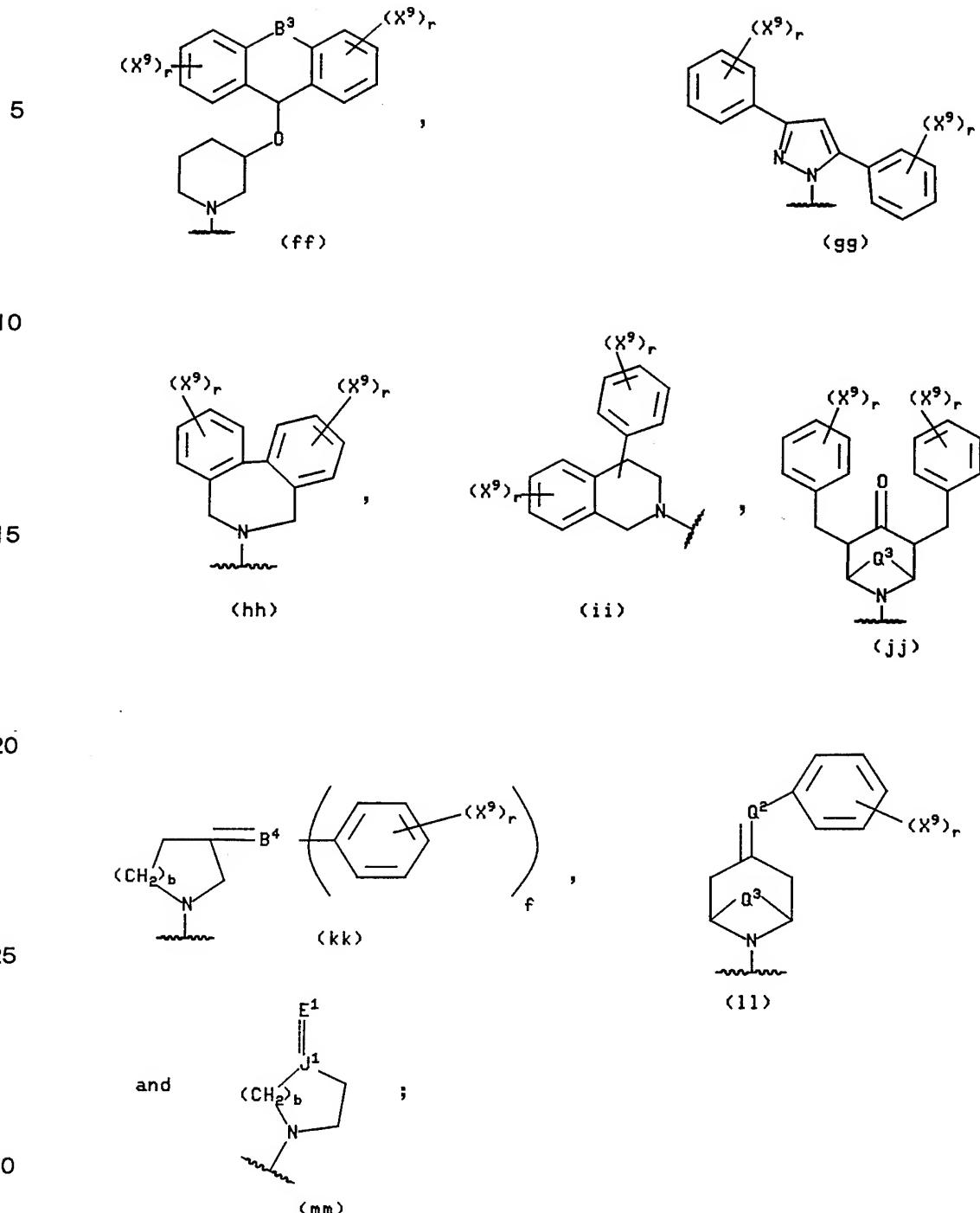
25



30

35

-138-



where X^9 , b , B^3 and r are as defined above;

Q^2 is selected from the group consisting of S, O, CH_2 and CH;

Q^3 is (C_1-C_4) alkylene;

B^4 is selected from the group consisting of C, O, $CH-CN$, CH and CH_2 ;

35

-139-

f is 1 or 2;

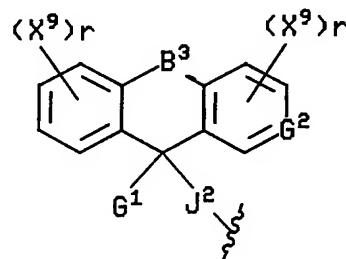
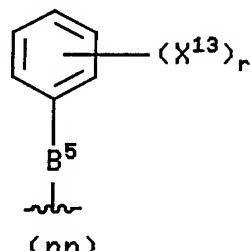
J¹ is selected from the group consisting of C, CH, and N;

— represents a single or a double bond,

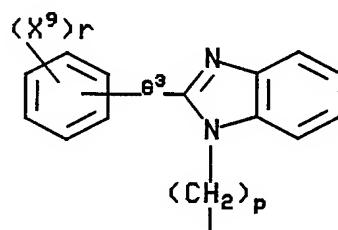
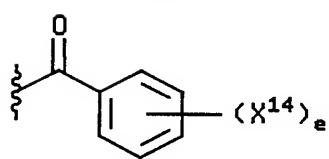
5

and E¹ is selected from the group consisting of alkylphenyl having 1 to 4 carbons,

10



15

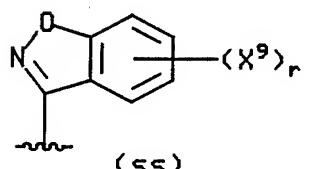
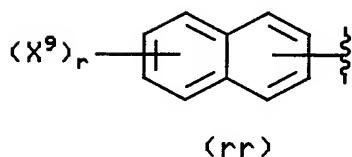


20

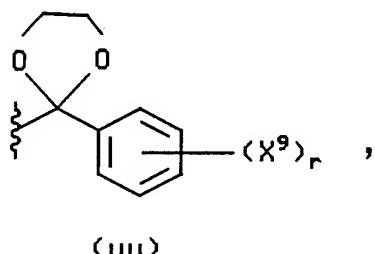
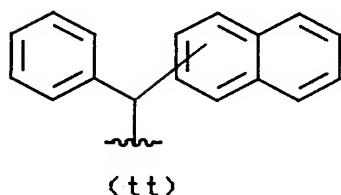
(pp)

(qq)

25

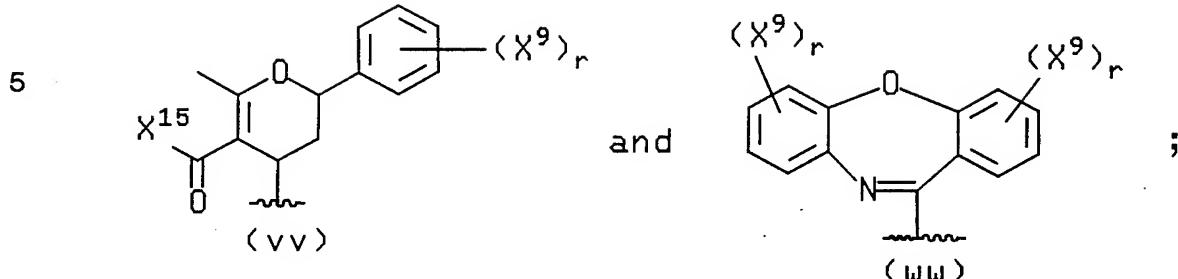


30



35

-140-



where X⁹, B³ and r are as defined above;

B⁵ is O, S, a covalent bond, CH, C=O, or (C₁-C₃)alkylene;

X¹³ is selected from the group consisting of hydrogen,

hydroxy, chloro, fluoro, (C₁-C₄)alkoxy, CF₃, (C₁-C₄)alkyl

15 and thioalkyl having 1 to 4 carbons;

G¹ is hydrogen, CN or hydroxy;

G² is N or CH;

J² is selected from the group consisting of C=O, a covalent bond and (C₁-C₄)alkylene;

20 X¹⁴ is, for each occurrence, independently (C₁-C₄)alkyl;

e is 2, 3, 4 or 5;

G³ is $\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}- \text{ or } -\text{C}-\text{NH}- \end{array}$;

25 and p is 2 or 3;

provided that:

(1) when Y¹ is a covalent bond or when n is 0, Z¹ cannot be hydroxy, NO₂, -S(C₁-C₄)alkyl or -O(C₁-C₄)alkyl;

(2) B¹ and A¹ cannot each be a covalent bond;

30 (3) when B¹ is an optionally substituted phenyl, Q¹ is selected from the group consisting of structures (a), (b), (c), (d), (e), (f), and (g);

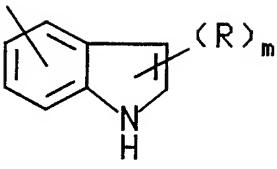
(4) R¹⁰¹ and R¹⁰² cannot both be hydrogen at the same time;

(5) when B¹ is a covalent bond and Y² is O, S, NH or $\begin{array}{c} -\text{C}-\text{N}- \\ \parallel \\ \text{H} \end{array}$, A¹ is not O, S or NH;

35

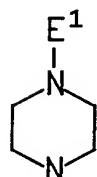
-141-

5

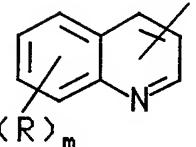
(6) when Q^1 is  , R^{101} and R^{102} taken together with the nitrogen to

10

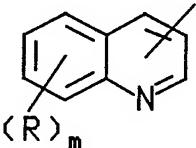
which they are attached cannot be



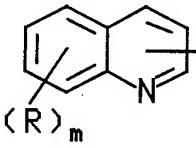
15

(7) when Q^1 is  and R^{102} is hydrogen, R^{101} cannot be alkylphenyl having

20

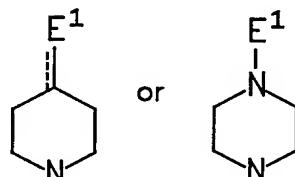
(8) when Q^1 is  and R^{101} is hydrogen, R^{102} cannot be (v), (w) or (y);

25

(9) when Q^1 is  , R^{101} and R^{102} taken together with the nitrogen to

30

which they are attached cannot be

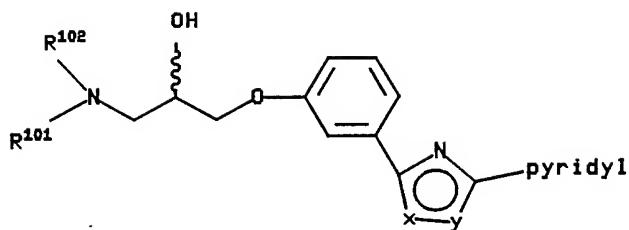
wherein E^1 is (nn) or (oo);

35

(10) when the compound of formula (I) is

-142-

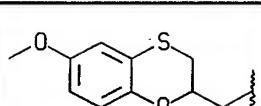
5



10 wherein X is N and Y is O or X is O and Y is N then R¹⁰¹ and R¹⁰² taken separately or together with the nitrogen to which they are attached cannot be the following:

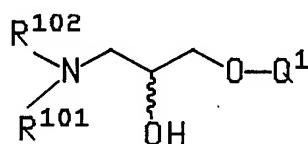
	R ¹⁰¹	R ¹⁰²	R ¹⁰¹ and R ¹⁰² taken together with the N to which they are attached
15 a	-	-	
20 b	-	-	
25 c	H		-
30 d	H		-
35 e	H		-
f	H		-
g	H		-

-143-

	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
5	h n-butyl		

(11) when the compound of formula (I) is

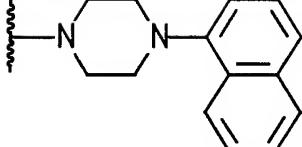
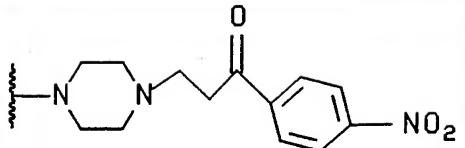
10



15

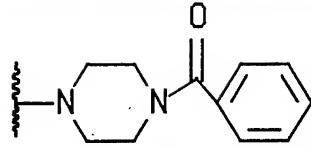
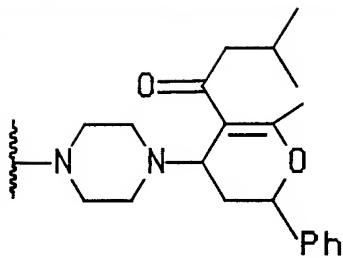
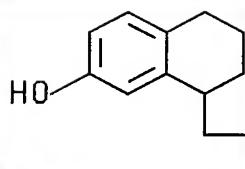
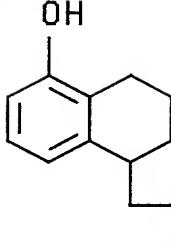
wherein Q^1 is quinolin-5-yl or 2-methylbenzthiazol-7-yl, then R^{101} and R^{102} taken separately or together with the nitrogen to which they are attached cannot be the following:

20

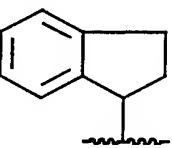
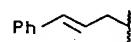
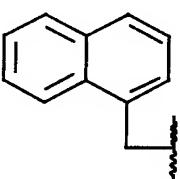
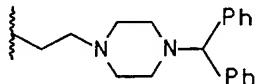
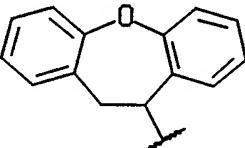
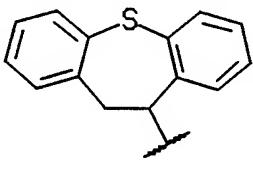
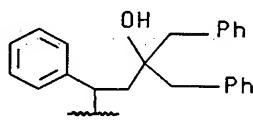
	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
25	a -	-	
30	b -	-	

35

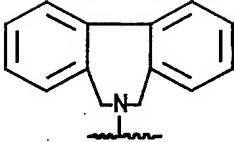
-144-

	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
5	c	-	
10	d	-	
15			
20	e	H	
25	f	H	
30			

-145-

	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
5	g H		
10	h 		
15	i H		
20	j H		
25	k H		
30	l H		

-146-

	R^{101}	R^{102}	R^{101} and R^{102} taken together with the N to which they are attached
5	m	-	
10			

(12) when R^{102} is (u), and A^2 is a covalent bond, Z^3 cannot be hydroxy;

(13) when R^{101} and R^{102} are taken together with the nitrogen to which they are attached and forms (mm) and b is 1, J^1 cannot be nitrogen;

15 (14) the compound of the formula (I) is not methyl-[3-(2-methyl-benzothiazol-7-yloxy)-propyl]-naphthalen-1-ylmethyl-amine;

(15) the compound of the formula (I) is not 1-(4-diethylamino-2-methyl-benzothiazol-7-yloxy)-3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-propan-2-ol;

20 (16) the compound of the formula (I) is not 1-(6-allyl-2-methyl-benzothiazol-7-yloxy)-3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-propan-2-ol; and

(17) the compound of the formula (I) is not 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(6-methoxy-2-phenyl-benzothiazol-7-yloxy)-propan-2-ol.

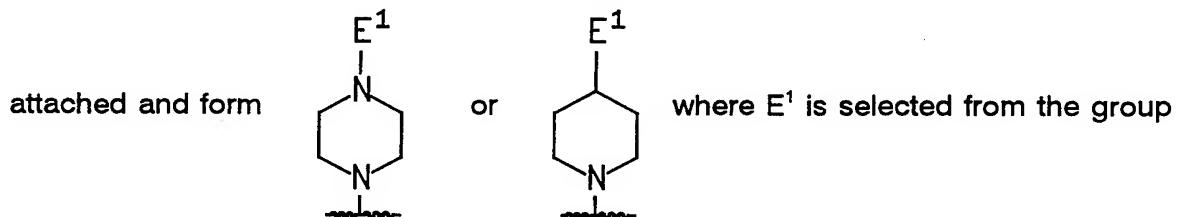
2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein B^1 is an optionally substituted phenyl; Y^2 is attached to B^1 in an ortho or meta position relative to A^1-Q^1 ; A^1 is selected from the group consisting of a covalent bond, O, S and $-CH_2-$; and Q^1 is selected from the group consisting of (a), (b), (c) and (d).

3. A compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein A^1-Q^1 is attached to the optionally substituted phenyl in the ortho position relative to Y^2 ; Y^1 is $-CH_2-$; Z^1 is hydrogen; n is 1 or 2; and Y^2 is selected from the group consisting of O, NH, NCH_3 and S.

4. A compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein A^1 - Q^1 is attached to the optionally substituted phenyl in the meta position relative to Y^2 ; Y^1 is $-CH_2-$; Z^1 is hydrogen or $-OH$; n is 1 or 2; and Y^2 is selected from the group consisting of O, NH, NCH_3 and S.

5 5. A compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein A^1 is a covalent bond; Q^1 is (c); m is 1; and R is selected from the group consisting of pyridin-3-yl and pyridin-4-yl.

10 6. A compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein R^{101} and R^{102} are taken together with the nitrogen to which they are



consisting of (nn), (oo), (pp) and (qq).

20 7. A compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein R^{101} is selected from the group consisting of hydrogen, alkenylphenyl having 2 to 4 carbons, and alkylphenyl having 1 to 4 carbons in the alkyl portion and optionally substituted at the phenyl portion; R^{102} is selected from the group consisting of (p), (s), (u), (v) and (w); Z^1 is $-OH$; n is 1; and Y^2 is O.

25 8. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein B^1 is a covalent bond and Q^1 is (g), wherein X^2 is N; X^3 is CR or N; and X^4 is S or O.

9. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein B^1 is a covalent bond and Q^1 is (g), wherein X^2 is N; X^3 is S or NR; and X^4 is N.

30 10. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein B^1 is a covalent bond and Q^1 is (g), wherein X^2 is N; X^3 is N or CR; and X^4 is NH or NCH_3 .

35 11. A compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein Y^1 is $-CH_2-$; Z^1 is hydrogen or $-OH$; n is 1 or 2; and Y^2 is selected from the group consisting of O, NH, NMe and S.

-148-

12. A compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein Y^1 is $-CH_2-$; Z^1 is hydrogen or $-OH$; n is 1 or 2; and Y^2 is selected from the group consisting of O, NH, NMe and S.

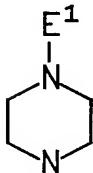
5 13. A compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein Y^1 is $-CH_2-$; Z^1 is hydrogen or $-OH$; n is 1 or 2; and Y^2 is selected from the group consisting of O, NH, NMe and S.

10 14. A compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein Y^1 is O, Z^1 is hydrogen; n is 1; and Y^2 is O.

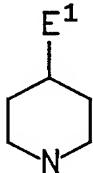
15 15. A compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein Y^1 is O, Z^1 is hydrogen; n is 1; and Y^2 is O.

16. A compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein Y^1 is O, Z^1 is hydrogen; n is 1; and Y^2 is O.

15 17. A compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein Z^1 is $-OH$; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the nitrogen to which they are attached and is selected from the group consisting of

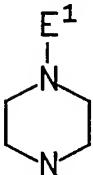


and

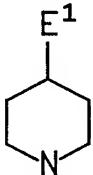


wherein E^1 is selected from the group consisting of (nn), (oo), (pp) and (qq).

25 18. A compound according to claim 12, or a pharmaceutically acceptable salt thereof, wherein Z^1 is $-OH$; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the nitrogen to which they are attached and is selected from the group consisting of



and

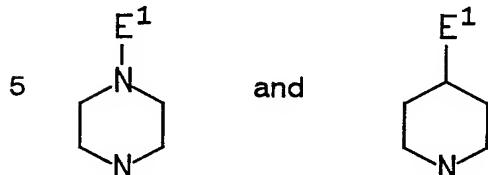


wherein E^1 is selected from the group consisting of (nn), (oo), (pp) and (qq).

35 19. A compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein Z^1 is $-OH$; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the

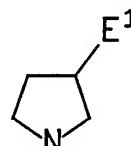
-149-

nitrogen to which they are attached and is selected from the group consisting of



wherein E^1 is selected from the group consisting of (nn), (oo), (pp) and (qq).

10 20. A compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the

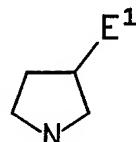
nitrogen to which they are attached and is  wherein E^1 is (oo).

15 21. A compound according to claim 12, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the

20 20. A compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the



25 22. A compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the

nitrogen to which they are attached and is  wherein E^1 is (oo).

30 23. A compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the nitrogen to which they are attached and is selected from the group consisting of (bb), (ee) and (ff).

35 24. A compound according to claim 12, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the

-150-

nitrogen to which they are attached and is selected from the group consisting of (bb), (ee) and (ff).

5 25. A compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{101} and R^{102} are taken together with the nitrogen to which they are attached and is selected from the group consisting of (bb), (ee) and (ff).

10 26. A compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{102} is selected from the group consisting of (l), (n), (o), (p), (s), (u) and (x).

15 27. A compound according to claim 12, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{102} is selected from the group consisting of (l), (n), (o), (p), (s), (u) and (x).

20 28. A compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein Z^1 is -OH; n is 1; Y^2 is O; and R^{102} is selected from the group consisting of (l), (n), (o), (p), (s), (u) and (x).

25 29. The compounds according to claim 1, or the pharmaceutically acceptable salts thereof, said compounds being

20 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(3-methyl-3H-benzoimidazol-4-yloxy)-propan-2-ol,

1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(3-methyl-3H-benzotriazol-4-yloxy)-propan-2-ol,

1-(benzothiazol-7-yloxy)-3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-propan-2-ol,

25 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

1-(4-benzhydryl-piperidin-1-yl)-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

30 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-dimethylamino-benzothiazol-7-yloxy)-propan-2-ol,

7-{3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-benzothiazole-2-carboxylic acid amide,

1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-pyridin-3-ylbenzothiazol-7-yloxy)-propan-2-ol,

35 1-(4-benzhydryl-piperidin-1-yl)-3-(2-pyridin-2-yl-benzothiazol-7-yloxy)-propan-2-ol,

1-(2-methyl-benzothiazol-7-yloxy)-3-[4-(2-propylsulfanyl-phenyl)-piperazin-1-yl]-propan-2-ol,

5 N-[1-(3-{4-[2-hydroxy-3-(2-methyl-benzothiazol-7-yloxy)-propyl]-piperazin-1-yl}-propyl)-1H-benzoimidazol-2-yl]-4-methoxy-benzamide,

10 1-(5-chloro-tricyclo[7.3.1.0,2,7]trideca-2,4,6,10-tetraen-13-ylamino)-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

15 3-[2-hydroxy-3-(2-methyl-benzothiazol-7-yloxy)-propylamino]-2-phenyl-decahydro-naphthalen-2-ol,

20 1-(4-benzhydryl-piperazin-1-yl)-3-[3-(5-pyridin-3-yl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol,

25 1-(4-benzhydryl-piperidin-1-yl)-3-[3-(5-pyridin-3-yl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol,

30 1-(4-benzhydryl-piperidin-1-yl)-3-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol,

35 1-(4-benzhydryl-piperidin-1-yl)-3-[3-(3-pyridin-3-yl-[1,2,4]oxadiazol-5-yl)-phenoxy]-propan-2-ol and

40 1-(methyl-naphthalen-1-ylmethyl-amino)-3-[3-(3-pyridin-3-yl-[1,2,4]oxadiazol-5-yl)-phenoxy]-propan-2-ol.

30. The compounds according to claim 1, or the pharmaceutically acceptable salts thereof, said compounds being

1-[4-(2-chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

25 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol,

30 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-dimethylamino-benzothiazol-7-yloxy)-propan-2-ol,

35 7-{3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-2-hydroxy-propoxy}-benzothiazole-2-carboxylic acid amide,

1-[4-[2-hydroxy-3-(2-methyl-benzothiazol-7-yloxy)-propyl]-piperazin-1-yl]-2,2-diphenyl-ethanone,

1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-pyridin-4-yl-benzothiazol-7-yloxy)-propan-2-ol,

35 1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(2-isopropyl-benzothiazol-7-yloxy)-propan-2-ol,

-152-

1-(2-butyl-benzothiazol-7-yloxy)-3-(1-phenyl-cyclohexylamino)-propan-2-ol,
1-(2-butyl-benzothiazol-7-yloxy)-3-[1-(4-chloro-phenyl)-cyclohexylamino]-propan-2-ol,
5 1-(4-benzhydryl-piperidin-1-yl)-3-[3-(5-pyridin-3-yl-[1,2,4]oxadiazol-3-yl)-phenoxy]-
propan-2-ol,
1-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazin-1-yl]-3-(3-methyl-3H-
benzoimidazol-4-yloxy)-propan-2-ol,
1-(4-benzhydryl-piperidin-1-yl)-3-(2-methyl-benzothiazol-7-yloxy)-propan-2-ol and
10 3-[2-hydroxy-3-(2-methyl-benzothiazol-7-yloxy)-propylamino]-2-phenyl-decahydro-
naphthalen-2-ol.

15 31. A method of inhibiting a P-glycoprotein in a mammal in need of such treatment which comprises administering to said mammal a P-glycoprotein inhibiting amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

32. A method of claim 31, wherein the mammal is a human suffering from cancer and said compound is administered before, with or after the administration to said human of an anticancer effective amount of a chemotherapeutic agent.

20 33. A pharmaceutical composition for administration to a mammal which comprises a P-glycoprotein inhibiting amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier and, optionally, an anticancer effective amount of a chemotherapeutic agent.

25

30

35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/01724

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D277/64 A61K31/425 C07D277/66 C07D417/14 C07D235/06
C07D249/18 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 363 212 (MITSUI TOATSU CHEMICALS INCORPORATED) 11 April 1990 cited in the application see claims ---	1,31-33
A	EP,A,0 224 086 (BAYER AG) 3 June 1987 see claims ---	1,31-33
A	EP,A,0 511 790 (AJINOMOTO CO LTD) 4 November 1992 see claims ---	1,31-33

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

1

Date of the actual completion of the international search 28 June 1994	Date of mailing of the international search report 15.07.94
---	--

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/01724

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 117, no. 23, 7 December 1992, Columbus, Ohio, US; abstract no. 233859m, page 857 ; see abstract & JP,A,4 134 070 (MITSUI TOATSU CHEMICALS INCORPORATED) 7 May 1992</p> <p>---</p>	1,31-33
A	<p>CHEMICAL ABSTRACTS, vol. 113, no. 13, 24 September 1990, Columbus, Ohio, US; abstract no. 109311e, page 79 ; see abstract & JP,A,2 121 924 (MITSUI TOATSU CHEMICALS INCORPORATED) 9 May 1990</p> <p>---</p>	1,31-33
A	<p>WO,A,92 18089 (THE UPJOHN COMPANY) 29 October 1992 see claims</p> <p>-----</p>	1,31-33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/01724

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
REMARK : ALTHOUGH CLAIMS 31-33 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN BODY. THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUNDS.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
THE FORMULATION OF THE CLAIMS IS SO COMPLICATED, BECAUSE OF THE DISTINCT COMBINATIONS OF THE MEANINGS OF THE VARIABLE PARTS THAT IT DOES NOT COMPLY WITH ART. 6 PCT PRESCRIBING THAT THE CLAIMS SHALL BE CLEAR AND CONCISE. FOR THESE REASONS THE SEARCH HAS BEEN LIMITED TO THE EXAMPLES.
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US 94/01724

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0363212	11-04-90	JP-A- US-A- US-A-	3101662 5112817 5204348	26-04-91 12-05-92 20-04-93
EP-A-0224086	03-06-87	DE-A- AU-B- AU-A- JP-A- US-A-	3617183 590024 6537586 62120365 5006534	27-05-87 26-10-89 21-05-87 01-06-87 09-04-91
EP-A-0511790	04-11-92	JP-A- US-A-	5117235 5292757	14-05-93 08-03-94
JP-A-4134070	07-05-92	NONE		
JP-A-2121924	09-05-90	NONE		
WO-A-9218089	29-10-92	AU-A- EP-A-	1773892 0579754	17-11-92 26-01-94